RECORD OF MEDICINE

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VOL. 168 NO. 1 JANUARY 1955

SYMPOSIUM ON MOTION SICKNESS. PART II

Guest Editor—MAJOR HERMAN I. CHINN, USAF

MEDICATION FOR MOTION SICKNESS PRIOR TO, AND DURING WORLD WAR II — *R. L. Noble*

THE NEWER THERAPY OF MOTION SICKNESS — *Herman I. Chinn and Paul K. Smith*

SIDE EFFECTS OF REMEDIES FOR MOTION SICKNESS — *E. M. Glaser*

SOME EFFECTS OF MOTION SICKNESS REMEDIES UPON PSYCHOLOGIC PERFORMANCE — *Robert B. Payne*

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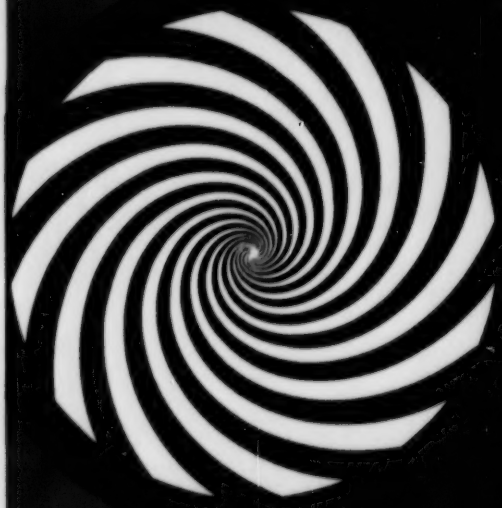

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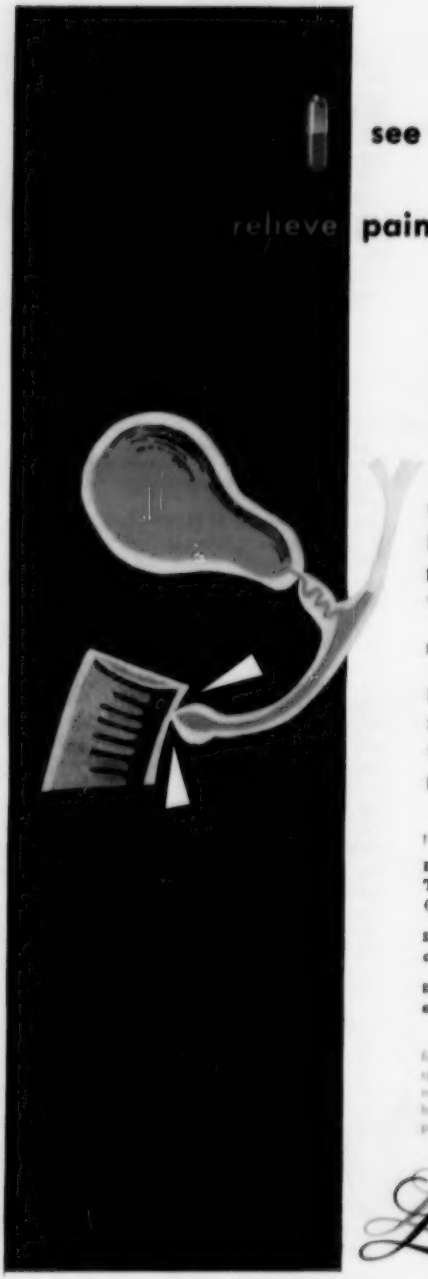

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Guest Editor—MAJOR HERMAN I. CHINN, USAF

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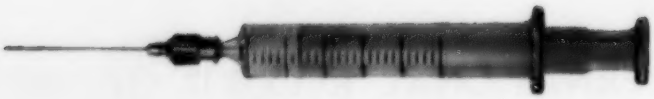

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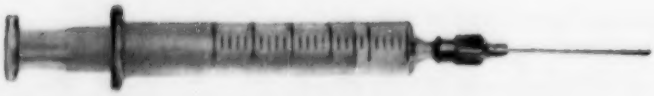

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SYMPOSIUM ON MOTION SICKNESS
PART II*

Medication for Motion Sickness Prior to and During World War II

R. L. Noble, M.D., Ph.D., D.Sc., F.R.S.C.†

LONDON, ONTARIO

Until the stimulus to research created by World War II, little of a scientific nature could be found relating to the treatment of motion sickness. Considering that the condition has been recognized since the time of antiquity, and that the symptoms of the afflicted were dreaded, it is surprising that more serious studies of the condition were not reported earlier. Because recent reports of treatment have been of necessity directed more toward military personnel, it should be appreciated that such types of therapy have had to be devoid of any side effects such as sedation, etc., which might lead to reduced efficiency in warfare; yet such actions might be quite acceptable for treatment of the ordinary sufferer. Treatment of the soldier and the civilian may therefore be different problems embracing the use of different drugs, different dosage, and different routes of administration. The former individual offers the greater challenge to the pharmacologist, since all the present known forms of drug therapy may give rise to untoward side effects and in doses not greatly in excess to those required for therapeutic action. A completely effective drug for human use has yet to be discovered.

Specific therapy may be directed at the use of a prophylactic measure to prevent the onset of sickness, at the treatment of the symptoms once they have developed, or

* Part I of the Symposium on Motion Sickness appeared in the December, 1954, issue of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS.

† Professor and Associate Director, Department of Medical Research, Collip Medical Research Laboratory, University of Western Ontario.

at the possibility of enhancing the rate of development of normal adaptation to motion. Most drug trials to be reported here have dealt with the prevention of motion sickness. The treatment of the established malady, while obviously of less practical application to large numbers of military personnel, introduces increasingly difficulty variables in evaluating therapy and practically eliminates the general use of an orally administered drug. The possibility of affecting adaptation by drugs has been little investigated.

The evaluation of any form of treatment and the comparison of different groups of results is a complex problem of almost insurmountable variables. Of primary importance is that the intensity and type of stimulus causing sickness be constant for any comparative test. This can only be accomplished by the use of some artificial device such as a swing or rocker. In sea or air trials the constancy of natural conditions cannot be controlled, and furthermore the intensity of the stimulus varies in different parts of the ship or aircraft. The head and body position of the individual subjects is similarly important and has to be controlled as far as possible. Spontaneous alterations in susceptibility and in the development of adaptation in addition must be considered. Because of the failure to appreciate such variables, most of the results of the authors of older papers cannot be properly evaluated. As an example one may find reported small groups of patients who stated that in preceding trips they had experienced nausea and to whom were administered some drug. When apparent success was achieved it was attributed to the drug without considering possible changes in the severity of weather conditions, the type of motion, the relative position of the patient or the ability of the individual to become ill consistently and the ease with which he physiologically adapted to motion. As a result, it is not surprising to find many forms of therapy advocated for motion sickness—many of these are different drugs but also various physical devices. To review these would be of historical interest only. In light of modern knowledge, however, it is of interest to note that some devices recommended were at least of potential value. The cause of motion sickness would seem directly related to stimulation of the labyrinth of the internal ear; with the possibility that the otolith is primarily affected. Destruction of these areas experimentally or from disease in experimental animals or humans renders a permanent immunity to motion sickness. The intimation that the nausea and vomiting caused by other conditions such as anesthesia, radiation, pregnancy, etc. are of the same etiology as motion sickness and may be expected to respond to the same therapy must be regarded with suspicion. Dogs rendered immune to motion sickness by ablation of the vestibular apparatus continue to show the characteristic vomiting after apomorphine. Because of the central mechanism involved in motion sickness it might be anticipated that drugs acting on the nervous system would prove the most effective, as has indeed been found.

The symptoms of sickness originate from labyrinthine stimuli apparently induced by motion and particularly by changes in linear acceleration. The effects of simple rotation are not usually considered under the term of motion sickness. The absence of nystagmus in true motion sickness divorces it from the latter condition. The motion induced by a simple swing, elevator or rocker, therefore, is essentially as effective as that imparted by a boat or aircraft. The symptoms in general may be re-

ferred to the gastrointestinal tract, the respiratory system, the cardiovascular system, and central nervous system. It is proposed to review and discuss therapy as it affects the various systems under the above headings.

Gastrointestinal Tract. The salivation, epigastric awareness, nausea, retching and vomiting associated with motion sickness suggested to many workers that the illness was directly related to the gastrointestinal tract. There would seem to be little to support such an implication. Most reports of studies on dogs and humans show that motion has a depressing effect on the gastric musculature, so that a loss of tone and reduction in peristalsis is associated with susceptibility.[1, 2] The sensation of nausea apparently occurs at this period of gastric immobility.[3] McDonough and Schneider concluded that "there is no specific type of gastrointestinal tract, either from an anatomic or functional standpoint, which is associated with motion sickness susceptibility." Such conclusions eliminate the older concept that states of "vagatonia" or "sympatheticotonia" are related to susceptibility and reduce the possibility that drugs acting locally on the stomach would prove to be effective agents. It is perhaps not surprising to find many recommendations of various foods, drinks, and dietary regimens for the susceptible individual. These vary from total fasting to the exclusive consumption of everything from fruit juices to beefsteak. Various alcoholic beverages have been recommended or condemned. Whereas their liberal use may lead to some indifference to the symptoms, any benefit may be related to the subsequently necessitated recumbent posture. Most evidence indicates that illness will occur irrespective of the amount of food in the stomach, and as long as the diet is not one to provoke indisposition in normal circumstances it makes little difference what or when food is eaten.[4–7] Visceral displacement has been suggested over the decades as a causative factor in motion sickness. Although such displacement may possibly occur there is no recent evidence to support that this is an important factor. The use of abdominal binders to prevent visceral displacement and shifts of blood to the abdomen has not been found to be of benefit in controlled studies.[8, 9] Severe protracted vomiting and lack of food and fluid intake in highly susceptible individuals may result in dehydration, ketosis, and alkalosis with characteristic findings. Such symptoms when they occur may be treated in the orthodox manner.[10]

The Respiratory System. The respiratory changes associated with motion sickness in humans are slight. There is usually a slight decrease in respiratory rate and a tendency to sigh and yawn. An occasional highly susceptible subject may respond by hyperventilation and even show signs of alkalosis and tetany.[11, 12] Dogs and cats, when exposed to motion, usually respond by an increase in frequency and amplitude of respiratory movements, but without significant changes in blood CO_2 or O_2 content.[13–16] Remedial methods of attempting to alter the rate or depth of respiration or to synchronize it with movements of the ship would appear to be of little value. Most sufferers apparently find some relief by exposure to fresh air, such as obtained on a boat deck. This may be related to their withdrawal from offending visual or olfactory stimuli or to an alteration in the type of motion on that part of the ship. Cold air *per se* is apparently of no benefit, since no significant difference in the incidence of swing sickness in hot and cold environments has been found.[7]

The Cardiovascular System. The chief symptom referable to this system is the intense

facial pallor associated with cold sweating, which occurs shortly before the nausea and vomiting. Of the various indications of sickness these appear to be the most reliable and constant.[18] The heart rate and blood pressure show only small variation during the development of sickness,[11, 19, 20] and it has been concluded that susceptibility to motion sickness cannot be related to any specific cardiovascular response to effective motion.[21] Attempts to relate the onset of sickness to alterations in cerebral blood flow and methods designed to prevent such changes have not been convincing. Anoxia comparable to that experienced at 10,000 feet altitude was not found to increase the incidence of swing sickness.[22]

Biochemical Changes in the Blood. Studies on dogs and man have failed to demonstrate that effective motion results in any consistent primary changes in blood chemistry that could be used to evaluate therapeutic action.[23–25]

THE CENTRAL NERVOUS SYSTEM

A. Psychologic Factors

The importance of psychic factors in the causation and control of motion sickness has been endorsed by a number of workers.[26–32] Tyler and Bard,[22] in a critical review on this subject, have concluded, however, that "the results of relevant, adequately controlled studies do not permit the conclusion that psychologic or psychopathologic factors are of importance in the etiology of motion sickness." Furthermore, their review of the effects of treatment of swing, sea, or air sickness by placebos do not suggest that appreciable protection is afforded by nonspecific remedies. Since there is little acceptable evidence that psychologic or emotional factors are of significance in the cause of motion sickness, the results of psychotherapy hold little promise for treatment of this condition.[22]

In a susceptible individual who is suffering from any degree of motion sickness, however, it should be emphasized that any normally nauseating stimuli may aggravate the condition. Thus, disagreeable sights, such as others vomiting, visual disturbances, and nauseating odors, should be avoided. Mental activity or distraction is apparently of little benefit, since aerial navigators and radio operators show the highest sickness rates found in an air crew.[30, 32]

B. Adaptation

The large majority of susceptible individuals eventually adapt to motion if the exposure is continued. This physiologic mechanism is not well understood, although it appears from experiments on dogs that adaptation occurs more rapidly and lasts longer in animals of lowest susceptibility to motion. Extreme susceptibility is associated with the slow development of transitory adaptation and only after almost continuous exposure to motion.[22] Probably fewer than 1 per cent of susceptible persons do not show at least partial adaptation to motion sickness, and temporary symptomatic therapy is usually followed by the gratifying effects of adaptation. Adaptation is highly specific for any type of motion experienced and should not be expected to give protection for more than a short period of days after the exposure

to motion is discontinued. Thus adaptation to seasickness may not be assumed necessarily to protect against airsickness. For this reason various types of machines and exercises designed to adapt individuals to motion before travelling by ship or plane have not proved of value.[34, 35] No drug therapy has yet been suggested to facilitate adaptation, although the process can proceed normally in susceptible dogs even though they be protected against actual sickness by barbiturate therapy.[36]

C. Vestibular Reactions

Since the chief factor causing the onset of motion sickness is a stimulation of vestibular receptors it might be expected that certain physical means might possibly reduce such stimulation. Carefully planned studies have now shown that head position may greatly modify susceptibility to this disease. For example, on swings the incidence of sickness was found to be 0 per cent when the subject was lying supine with the occiput slightly tilted back, but rose to 68 per cent if the head was flexed forward. Similarly, in the sitting position an incidence of 61 per cent sickness was reduced to 0 per cent by simply tilting the head backwards.[37] Other reports show the same general results. Such alterations in susceptibility due to changes in positions of the head have suggested that the utricles are the part of the vestibular apparatus predominantly affected by motion (see review by Tyler and Bard[21]). More recent work has indicated that small head movements induced by motion are important stimuli.[38] Visual stimuli may help the individual to compensate for exciting head movements and so be of benefit. Visual orientation with the ground or horizon and compensatory head movement probably explains why those piloting an aircraft or those going outside on a boat deck have a reduced incidence of sickness. Changes of body position appear of less importance to the onset of sickness, except when they may allow visual orientation to take place. Thus, soldiers crouched in landing craft showed a 30 per cent incidence of sickness compared with only 11 per cent in those standing upright who could see the horizon.[39] The ideal resting position for a susceptible individual, therefore, is flat in bed, the head if possible being tilted slightly back, but not raised forward by a pillow. If seated, the head should be tilted as far back as possible on a head rest—it is of some interest that the usual deck chair allows the head to approach a position associated with a reduced incidence of seasickness. The use of headrests on seats to fix the head may be practical in specialized circumstances in aircraft.[40]

Drug Therapy

No attempt has been made in this article to review the wide assortment of drugs recommended for medication and described by Tyler and Bard[21] to include nearly every item in the pharmacopoeia. In nearly all cases the assessment of their true efficacy in view of the now known variables is quite impossible. In defense of these older papers, however, it must be pointed out that the types of drugs proved by recent trials to have therapeutic value had previously been recommended by numerous investigators and were even contained in a number of widely used proprietary seasick preparations. The investigations during the period of the second World War simply

proved scientifically that various belladonna alkaloids and barbituric acid derivatives were actually effective forms of preventive therapy for motion sickness and made an estimate of their effectiveness. In addition they did disprove certain other classes of compounds thought to be active substances. Most of the tests and field trials conducted assessed the value of a single dose of the drugs as preventives of nausea and vomiting in young healthy male subjects. The little evidence available indicates that such active compounds might be expected to alleviate the symptoms if they can be given once illness had developed. Well-controlled tests have been conducted on humans using the motion of swings, aircraft or various sea vessels. Dogs have also been used for therapeutic tests; they differ from the human in that they do not show any beneficial effects of even large doses of the belladonna alkaloids but respond and tolerate better the effective barbiturates.[36, 41, 42] This evidence is strongly suggestive that the mode of action of these two classes of drugs in preventing motion sickness must be different and indicates that both types of therapy should be attempted in refractory patients and that a combined therapy might prove more efficacious.

A. Belladonna Alkaloids

These consist of hyoscine (scopolamine) and atropine, a mixture of the two optical isomers, *d*- and *l*-hyoscyamine. The latter isomer is the usual commercial product of hyoscyamine.

Hyoscine has proved to be the most effective agent of these alkaloids, when compared with the effects of a placebo. In tests on swings a single oral dose of 0.4 to 0.8 mg. of hyoscine hydrobromide given 1 to 2 hours prior to motion gave protection rates of from 29 to 76 per cent.[43–45] In sea trials the English workers have repeatedly found hyoscine the most effective agent. In 1944 they reported that 0.6 mg. of the hydrobromide protected 57 per cent of those who would have been ill if given a placebo. Larger doses, up to 1.2 mg. gave slightly more protection.[46] Others have also estimated the protection afforded by similar doses of hyoscine in sea trials and have found protection rates of 49 to 66 per cent. It appears from these results that, under rough weather conditions associated with a high incidence of vomiting in the placebo treated group, the effectiveness of hyoscine therapy is definitely less than under less severe conditions.[39, 47] Similarly, air sickness has been described as reduced by doses of 0.6 to 0.75 mg. of hyoscine hydrobromide. From 92 to 67 per cent protection was afforded, depending on the roughness of the flight.[48–50]

Atropine has been studied less extensively than hyoscine. In single oral doses of 1 mg. of the sulfate, protection rates of from 39 to 47 per cent in sea trials and swing tests have been obtained.[43, 46] Its activity, therefore, would seem definitely less than that of hyoscine.

l-*Hyoscyamine* has been administered alone in a number of tests. In one sea trial 0.96 mg. of the hydrobromide afforded 39 per cent protection. This was the same figure as that obtained for 1.0 mg. atropine but contrasted with 53 per cent protection from 0.6 mg. of hyoscine obtained by the same group of workers.[46] In swing tests *l*-hyoscyamine also proved to be somewhat less active than hyoscine.[44, 45]

d-*Hyoscyamine* has been tested in only 1 sea trial. The action of 2.0 mg. was to

protect only 25 per cent of susceptible individuals of a small group of 34.[45] This single experiment suggests that this isomer is considerably less active than the *l*-rotatory form of atropine.

Combined Belladonna-alkaloid Therapy. In an effort to reduce side actions various mixtures of belladonna alkaloids have been tested on swing, sea, and air trials (reviewed by Noble, Sellers, and Best).[45] The combination of *l*-hyoscyamine hydrobromide, 0.8 mg., and hyoscine hydrobromide, 0.3 mg., has been studied most extensively and was referred to during the war as the Royal Canadian Navy (RCN) remedy. Protection rates found in the various trials from this mixture were from 37 to 73 per cent, indicating an effectiveness approximately equal to the larger dose of 0.65 mg. of hyoscine when used alone.[39, 44, 47, 49, 51]

Other Belladonna-like Drugs. In single tests on small groups of individuals homatropine, 12 mg., benzoyltropine, 50 mg., and benzyoloscine, 50 mg., were only moderately active. Similarly, demerol, 100 mg., and pavatrine, 250 mg., were not concluded to be active.[42]

Side Actions of Belladonna Alkaloids. Although the general pharmacologic actions of this group of drugs is well known it was imperative that the doses used for military personnel should not impair efficiency. In general it may be stated that of the most effective agents, hyoscine and hyoscine+hyoscyamine mixtures, the doses of 0.65 mg. of the former and 0.3 mg. +0.8 mg. of the latter as hydrobromides did not give rise to serious side effects. Dryness of the mouth occurred in about one third of the treated individuals. When larger doses of the belladonna alkaloids are used—up to 1.5 mg. of hyoscine—marked drying of the mouth and throat occur. Sweating is reduced during exercise or exposure to heat. Increased heart rate and loss of visual accommodation and lowered visual efficiency may take place. Central actions may include drowsiness, "cloudiness," excitement, and hallucinations. It has been suggested that *l*-hyoscyamine is better tolerated than hyoscine.[7, 43, 45, 46, 48, 49, 52] Although some of the effects of the larger doses may not be considered as a deterrent to treating the civilian population, it should be appreciated that the above studies were made exclusively on young healthy active males. Whereas it is advisable to use the largest well-tolerated dose to achieve the best results, the actual dosage selected for elderly, sedentary, or invalid persons should be estimated individually by the experienced physician. Children have a lower tolerance than do adults.

Continued Doses. The results of continued belladonna-alkaloid therapy have not been seriously assessed, nor has an optimal dosage been established. It has been suggested that protection from a single dose lasts from 6 to 10 hours. The recommended subsequent dosage has been "not more than one-half the initial dose and separated by an interval of 8 hours or more."[48] Individuals should be cautioned that any undue dryness of the mouth, blurring of the vision, or unexpected symptoms indicating hypersensitiveness should be followed by a reduction or cessation of therapy.

B. Barbiturates

The use of barbiturates and other sedatives has been advocated by numerous investigators for the treatment of motion sickness. The evaluation of this older work

is again difficult, but it is perhaps best discussed in light of experience gained during the war years with these compounds. The first point that may be stressed is that motion sickness occurs only when the higher centers of the brain are functioning. Any hypnotic, therefore, if given in large enough dosage, will keep a susceptible individual drowsy or asleep and free of the subjective and objective symptoms. Such an action is not specific for the treatment of motion sickness. When smaller doses were used, as in the older literature, the individuals usually were told to lie down or go to bed. The resulting action, therefore, could not be attributable solely to the drug. Most of the commonly used barbiturates in ordinary dosage have not proved to be effective against swing or sea sickness. These include barbital, 325 mg.; pentobarbital, 100 mg.; Seconal, 50 and 100 mg.; Amytal, 65 mg.; phenobarbital, 65 mg.; and hexobarbitone, 650 mg.[14, 46, 53, 61] The possible exception is the report that 130 mg. Amytal gave protection to 39 per cent of susceptibles in a sea trial.[39]

Experimental studies on dogs have indicated that certain barbiturates may possess a high degree of activity in preventing swing sickness. This action was apparently specific and had no relationship to the hypnotic potency of the compounds. Effective doses did not cause any discernible symptoms in the dog. Even barbiturates, which were excitants causing convulsions in toxic doses in animals, possessed the property of inhibiting motion sickness. Such substances were believed to exert a specific central action depressant to the centers involved in causing motion sickness.[26] In such dog experiments the more commonly used barbiturates possessed little activity in preventing vomiting. From a number of the more highly active compounds, a sulfur-containing barbiturate, ethyl-β-methylallylthiobarbituric acid (Mosidal), was studied most extensively on humans. This compound, however, was less well tolerated by the human than by the dog, and doses of 390 mg. may cause drowsiness. (In the dog symptoms do not occur until doses approaching 30 mg./Kg. are used.) From a consideration of the various swing and sea trials with this substance it may be concluded that doses of 195 to 325 mg. are effective and approximate the effectiveness of hyoscine when the sickness rate of the control group was below 30 per cent. Under more severe conditions hyoscine was the better preventive. If therapy with this thiobarbiturate is prescribed, it is suggested that 2 daily doses of 163 mg. (2½ grains) taken with the morning and evening meal are best tolerated, and possibly more effective than a single dose of double this amount.

Combined Belladonna Alkaloid and Barbiturate Therapy. Probably the most effective drug combination developed prior to the war was a mixture of 65 mg. Amytal, 0.2 mg. hyoscine, and 0.16 mg. atropine. This was known as Motion Sickness Preventive, Army Development Type (MSP), and the usual dose was 2 capsules, each of the above dosage. Extensive tests on swing, sea, and air trials compared this mixture with the separate belladonna alkaloids and in some cases in combination with ethyl-β-methylallylthiobarbituric acid. These results showed that MSP (2 capsules), the RCN mixture (0.3 mg. hyoscine and 0.8 mg. *l*-hyoscyamine), and 0.65 mg. of hyoscine alone were all of equal effectiveness. Protection rates were found of from 92 per cent when the sickness rate of controls was only 5.1 per cent to 49 per cent when the sickness rate of controls was 53 per cent. Little evidence was seen that the addition of either amytal or the thiobarbiturate improved the effectiveness of the bella-

donna alkaloids.[7, 39, 44, 47, 49, 51, 54, 55] On swing tests occasional individuals are observed who may be protected by a barbiturate and not by hyoscine and *vice versa*, although most patients responded to either form of therapy.[44] Since in addition to this it seems apparent that the mode of action of these two classes of drugs is different, it seems reasonable to use a combined form of therapy. With this in mind, the "Canadian Motion Sickness Remedy—National Research Council Formula" was described as a capsule containing 0.1 mg. hyoscine, 0.3 mg. hyoscyamine, and 130 mg. ethyl-β-methylallylthiobarbituric acid. The recommended dose was 2 capsules to be taken 2 to 4 hours before exposure to motion and a single capsule every 8 to 12 hours thereafter. The toxicity of this mixture was negligible even when taken over a considerable period of time,[48, 51] although the usual precautions with individuals excessively susceptible to barbiturates must be kept in mind.

C. Other Substances

Various other substances have been tested for their effectiveness against motion, usually from swings. Large doses of the vitamins nicotinic acid, thiamine, or pyridoxine did not afford any protection.[44, 54] Similarly, benzedrine, ephedrine, and methedrine were not effective agents.[9, 46, 53, 54, 58] Prostigmine alone or prostigmine and syntropan were also quite ineffective.[39, 49]

SUMMARY OF THE SUGGESTED TREATMENT OF MOTION SICKNESS

General

Avoid food and drink normally causing indisposition. Avoid visual, olfactory, and other stimuli normally nauseating. Visual orientation with the ground or horizon when possible is desirable.

Head position is important. Lying in bed with the head flat or sitting with the head tilted well back are positions associated with the lowest incidence of sickness. In severe illness protracted vomiting may lead to dehydration, ketosis, and alkalosis. Alkalosis may also follow hyperventilation. Such symptoms require classic treatment.

Drugs

The best results on motion sickness have been reported from oral therapy with (1) 0.65 mg. hyoscine, (2) 0.3 mg. hyoscine + 0.8 mg. *l*-hyoscyamine. Theoretical consideration suggests the addition of a barbiturate may be of value, although improved protection over the belladonna alkaloids has not been demonstrated. Mixtures of approximately equivalent activity to hyoscine alone are (3) 130 mg. amytal, 0.4 mg. hyoscine, and 0.32 mg. atropine; or (4) 0.2 mg. hyoscine, 0.6 mg. hyoscyamine, and 260 mg. ethyl-β-methylallylthiobarbituric acid. The first dose should be taken orally 1 to 3 hours before exposure to motion; it acts for 8 to 10 hours. Continued dosage is usually half the above single dose taken every 8 to 12 hours.

The expected protection from treatment with any of the above four methods depends on the severity of the experienced motion. When the sickness rate in untreated

individuals is 5 per cent approximately 90 per cent of susceptibles should be protected. When 50 per cent of those untreated are ill about one-half of all susceptible treated individuals should be protected. Although doses above those recommended may improve the protection rate, the effect is probably not striking enough to justify the added possibility of toxic side effects.

Serious side effects have not been encountered in young healthy subjects with the above dosage. Larger doses of the belladonna alkaloids in normal persons or in patients with a decreased tolerance (children) may cause dryness of the mouth and throat, reduced sweating, visual disturbances, cardiac acceleration and mental excitement, cloudiness or even hallucinations. Overdosage with barbiturates may cause increasing drowsiness and respiratory depression. Sensitivity reactions may occasionally be encountered.

Susceptible individuals who do not respond to any therapy with the exception of some 1 per cent may be assured that ultimate improvement will occur through physiologic adaptation to the continued motion.

BIBLIOGRAPHY*

1. Barkin, B. P., and Bornstein, M. G.: The effect of swinging and of binaural galvanic stimulation on the motility of the stomach in dogs, Rev. Canad. de biol. 2:336, 1943.
2. McDonough, F. E., and Schneider, M.: Effect of motion on the roentgenographic appearance of the stomach and small bowel, Gastroenterology 2:32, 1944.
3. Wolf, S.: The relation of gastric function to nausea in man, J. Clin. Investigation 22:877, 1943.
4. Alexander, S. J.; Cotzin, M.; Hill, C. J., Jr.; Ricciuti, E. A., and Wendt, G. R.: Wesleyan University studies of motion sickness. Incidence of sickness at various hours of the day, J. Psychol. 20:19, 1945.
5. Best, C. H.; Sellers, E. A., and Stephenson, N. R.: Proc. of the Conference on Motion Sickness, National Research Council Canada, Report No. C735, Aug. 28, 1942.
6. Mannino, G. W., and Stewart, W. G.: Associate Committee on Aviation Medical Research, Canada, Report No. C2426, Dec. 1942.
7. Tyler, D. B.: Committee on Aviation Medicine, Final Report, National Research Council, 1946.
8. Aiken, J. B.; Hoffman, O., and Howlett, J. G.: Proc. of the Conference on Motion Sickness, National Research Council, Canada, Report No. 2506, June 16, 1943.
9. Brown, G. L.; McArdle, B., and Magladery, J. W.: British Flying Personnel Research Committee, Report No. 410a, 1941.
10. Marrack, J. R.: Ketosis in seasickness, Brit. M. J. 1:178, 1931.
11. Cipriani, A., and Morton, G.: Proc. of a Conference on Motion Sickness, National Research Council, Canada, Report No. C744, Aug. 28, 1942.
12. Rushmer, R. F.: Committee on Aviation Medicine, Report No. 157, National Research Council, May 1943.
13. Meakins, J. C.; Morton, G., and McEachern, D.: Proc. of a Conference on Motion Sickness, National Research Council, Canada, Report No. C747, Aug. 28, 1942.
14. Pozerski, E.: Appareil pour l'étude de l'influence des oscillations rhythmiques sur les animaux de laboratoire, Compt. rend. Soc. de Biol. 85:702, 1921.

* Throughout this article extensive use has been made of the excellent comprehensive review published in 1949 by Tyler and Bard. Detailed references may be obtained at this source. Since numerous publications on this subject were included in reports to various committees during the war and are not generally available, many of these have been omitted.

15. Sjöberg, A. A.: Experimentelle Studien uber den Auslosungsmechanismus der Seekrankheit, Acta Otolaryng. Supp. *14*:1, 1931.
16. Spiegel, E. A.: Respiratory reactions upon vertical movements, Am. J. Physiol. *117*:349, 1936.
17. Heminoway, A.: Environmental temperature and swing sickness, J. Aviation Med. *17*:86, 1946.
18. Heminoway, A.: Cold sweating in motion sickness, Am. J. Physiol. *141*:172, 1944.
19. Heminoway, A.: Cardiovascular changes in motion sickness, J. Aviation Med. *16*:417, 1945.
20. Maitland, T. G.: General observations on seasickness and the labyrinthine theory, Brit. M. J. *1*:171, 1931.
21. Tyler, D. B., and Bard, P.: Motion sickness, Physiol. Rev. *29*:311, 1949.
22. Fraser, A. M.: Associate Committee on Aviation Medical Research, National Research Council, Canada, Report No. C2644, Oct. 10, 1944.
23. Best, C. H., Sellers, E. A., Parker, J., and Stephenson, N. R.: Proc. of the Conference on Motion Sickness, National Research Council, Canada, Report No. C739, Aug. 28, 1942.
24. Babkin, B. P. S., Dworkin, S., and Schachter, M.: Experimental motion sickness and attempts at therapy, Rev. Canad. de biol. 5:72, 1946.
25. Fields, W. S., Meakins, J. C., and McEachern, D.: Proc. of a Conference on Motion Sickness, National Research Council, Canada, Report No. C740, Aug. 28, 1942.
26. Schwab, R. S.: Chronic seasickness, Ann. Int. Med. *19*:28, 1943.
27. McDonough, F. E., and Bond, D. D.: Management of the airsick aviator, Air Surgeon's Bull. *1*:Mar. 5, 1944.
28. Bond, D. D.: Committee on Aviation Medicine, Reports No. 147 and 158, National Research Council, Apr. 1943.
29. Rubin, H. J.: Airsickness in a primary airforce training detachment, J. Aviation Med. *13*:272, 1942.
30. Green, D. M.: Airsickness in bomber crews, J. Aviation Med. *14*:366 & 373, 1943.
31. Heminoway, A.: A.A.F. School of Aviation Med., Randolph Field, Texas, Project No. 381, Apr. 1945.
32. Levy, T.: Observations on airsickness, Mil. Surg. *93*:147, 1943.
33. Noble, R. L.: Adaptation to experimental motion sickness in dogs, Am. J. Physiol. *154*:443, 1948.
34. Gibson, W. C., Manning, G. W., and Cohen, E.: Assoc. Committee on Aviation Med. Research, National Research Council, Canada, Report No. C2638, Oct. 27, 1943.
35. Magladery, J. W.: British Military Personnel Committee Report No. 45, 1942.
36. Noble, R. L.: The effects of barbiturates and other substances on motion sickness in dogs, Canad. J. Research E *26*:283, 1948.
37. Howlett, J. G., Wardill, T. E. M., and Brett, J. R.: Proc. of the Conference on Motion Sickness, National Research Council, Canada, Reports No. 2507, 2508, June 16, 1943.
38. Johnston, W. H., Stubbs, R. A., Kelk, G. F., and Franks, W. F.: Stimulus required to produce motion sickness. Preliminary report dealing with importance of head movements, J. Aviation Med. *22*:1951.
39. Tyler, D. B.: The influence of a placebo, body position, and medication on motion sickness, Am. J. Physiol. *146*:468, 1946.
40. Johnston, W. H., and Mayne, J. W.: Stimulus required to produce motion sickness. Restriction of head movement as a preventive of airsickness—field studies in airborne troops, J. Aviation Med. *24*:400, 1953.
41. Babkin, B. P., and Dworkin, S.: Proc. of the Conference on Motion Sickness, National Resear h Council, Canada, Report No. 736, Aug. 28, 1942.
42. Hollino, H. E., and Trotter, W. R.: Military Personnel Research Committee, British Med. Research Council, Report No. WA520-7, Feb. 1943.
43. Smith, P. K., and Heminoway, A.: Effect of some atropine-like drugs on swing sickness, Proc. Soc. Exper. Biol. & Med. *63*:206, 1946.
44. Noble, R. L.: Treatment of experimental motion sickness in humans, Canad. J. Research E *24*:10, 1946.
45. Noble, R. L.; Sellers, E. A., and Best, C. H.: The treatment of motion sickness, Canad. M. A. J. *56*:417, 1947.
46. Hollino, H. E.; McArdle, B., and Trotter, W. R.: Prevention of seasickness by drugs, Lancet *2*:127, 1944.

47. Luyke, H. M. C.: Committee on Aviation Medicine, National Research Council, Report No. 306, Apr. 1944.
48. Lilienthal, J. L.: The effect of hyoscine on airsickness, J. Aviation Med. *16*:59, 1945.
49. Smith, P. K.: The effectiveness of some motion sickness remedies in preventing air sickness in airforce navigation students, J. Aviation Med. *17*:343, 1946.
50. Haslam, J. F. C.: Prevention of seasickness by drugs, Lancet *2*:804, 1944.
51. Parker, J. M.: Proc. of Associate Committee Naval Medical Research, National Research Council, Canada, Report No. C4116, Feb. 16, 1945.
52. Keil, F. C., Jr.: Committee on Aviation Medicine, National Research Council, Report No. 219, June 1943.
53. Sellers, E. A.; Parker, M. M., and Stephenson, N. R.: Proc. of Associate Committee on Naval Medical Research, National Research Council, Canada, Nov. 27, 1942.
54. Smith, P. K.: Effect of various substances on swing sickness, Proc. Soc. Exper. Biol. & Med. *63*:209, 1946.
55. Barrow, L. L.; Conn, H. F., and Williams, J. C.: Bulletin of the Sub-Committee on Motion Sickness, National Research Council, Apr. 1, 1943.
56. Park, J.: British Flying Personnel Research Committee Report No. 510, 1943.

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The Newer Therapy of Motion Sickness

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The therapy of motion sickness has been largely empiric or based upon outmoded theories that have long since been abandoned. The variety of medicaments, dietary recommendations, and prophylactic devices advocated through the years attests to the ingenuity of the medical profession and general populace alike. Typical examples are cited by Tyler and Bard[1] in their review and by Noble[2] in another paper in this Symposium. These examples can be multiplied manyfold by perusal of early medical journals. The lack of controlled observations is balanced by the enthusiastic recommendations. An added difficulty has been the use of complex mixtures, frequently before the individual components themselves had been tested.

It has generally been assumed that drugs effective against one type of motion sickness will be active in preventing other types as well. That this is not necessarily so is indicated by recent studies in which drugs markedly effective against airsickness and seasickness were without effect against swing sickness.[3] Still more hazardous is the use of animals for drug evaluation. Noble[4, 5] has shown atropine, hyoscine, and hyoscyamine to be without effect in dogs despite their marked usefulness in man. On the other hand, chlorpromazine protected a high percentage of dogs from becoming sick during swinging[6] but was ineffective in man—at least against seasickness (Handford et al[7]). Furthermore, the ability of a drug to prevent nausea and vomiting of other conditions—pregnancy, radiation, Menière's disease, drug administration, anesthesia, etc.—is no assurance that it will be of value against motion sickness. Until a compound has demonstrated its effectiveness in man under conditions of actual flight or sailing, it cannot be accepted as a motion sickness prophylactic regardless of its performance under other circumstances.

Since the early reports that hyoscine was effective against motion sickness,[8, 9] there has been ample confirmation that it provides excellent protection against seasickness[10, 11] and airsickness. Reports that hyoscine aminoxide, a partial oxidation product of hyoscine, had one third of the activity of hyoscine in Parkinson's disease with only one sixth of its toxicity[12] prompted its study against motion sickness. Two-milligram doses provided good protection both in airsickness and in seasickness,[13] but the side effects were as marked as would be expected from equivalent doses of hyoscine alone. A similar preparation, hyoscine *N*-bromobutylate (Buscopan), did not protect against seasickness.[14]

A number of synthetic antispasmodics with relatively little central nervous activity have been tested aboard ship with uniformly poor results. Methantholine (Banthine) bromide, propantheline (Probanthine) bromide, dicyclomine (Bentyl) hydrochloride,

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and hyoscine *N*-bromobutylate (Buscopan) all act upon smooth muscle and secretory glands innervated by postganglionic cholinergic fibers but were ineffective against seasickness.[15] These findings indicate that antimotion sickness effectiveness of parasympathetic drugs depends upon their actions on the central nervous system rather than the antispasmodic activity.

The use of central nervous system depressants to prevent motion sickness has remained popular throughout the years, perhaps because of one's obvious resistance to motion while sleeping or heavily sedated. A large variety of barbiturates have been tried with little effect.[8, 17, 18–21] Noble[22] has shown that the thiobarbiturate Mosidal protects man against swing sickness but other investigators could show no protection against seasickness.[16]

Vitamins have been tried sporadically, but only pyridoxine seems to have given promising results. Although Thuer[23] reported, without confirming data, that pyridoxine was ineffective in seasickness, Benkendorf[24] found 50 mg. by mouth to give marked relief in about one third of the 500 seasick subjects and mild improvement in another third. When pyridoxine was given by rectal suppository to 2,500 patients, 90 per cent showed improvement. Control patients receiving rectal placebos were not improved. Recently, Voss[25] has reported it to be of value against seasickness.

The discovery of dimenhydrinate (Dramamine) as a motion sickness prophylactic is well known to all.[26, 27] Its effectiveness against seasickness[28–26] and airsickness[37–41] has been rapidly and repeatedly confirmed. Despite the unequivocable evidence of the value of Dramamine, it is not superior to other available drugs. When 100 mg. of Dramamine were given before flight, 33 per cent of the subjects became sick, compared with only 20.4 per cent in the same aircraft receiving 0.65 mg. of hyoscine.[28] Similarly, no significant difference between Dramamine and hyoscine could be detected in protection against seasickness.[26]

Dramamine is the 8-chlorotheophyllin salt of β-dimethylaminoethylbenzohydryl ether, and Benadryl is the hydrochloride of the same base. On the basis of this close chemical similarity, Nickerson[42] predicted that the effects of both compounds should be the same. Direct comparison of Benadryl and Dramamine against seasickness[26, 43] and airsickness confirmed the accuracy of this prediction.[39]

Since Dramamine and Benadryl are antihistamines, it was at first thought that their ability to protect against motion sickness was a reflection of their antihistaminic potency. It was soon apparent, however, that not all antihistamines were effective. Phenindamine (Thephorin) tartrate,[26] Methaphenilene (Diatrin) hydrochloride,[15] dimethylaminoisopropylphenothiazine (Isophenergan) hydrochloride,[16] dimethylaminoethyl phenothiazine (Lisergan) hydrochloride,[16] and diethazine (Diparcol) hydrochloride were all without value in seasickness. Chlorprophenpyridamine (Chlor-Trimeton) and doxylamine (Decapryn) were relatively ineffective in the air,[18] and the reported protection with pyrilamine (Neo-Antergan) maleate[44, 45] or with chlortripelennamine (Synopen) hydrochloride could not be confirmed.[16]

Despite the inability of some antihistamines to afford protection, a large number of this group have proved excellent prophylactics. The phenothiazine derivatives

TABLE I

Drugs Effective in Motion Sickness Prophylaxis

Drug	Average Single Dose
Hyoscine hydrobromide	0.65–1.0
Dimenhydrinate (Dramamine)	100.
Diphenhydramine (Benadryl) hydrochloride	50.
Meclizine (Bonamine) hydrochloride	25.*
Cyclizine (Marezine) hydrochloride	50.
Prophenpyramine (Trimeton) maleate	25.
Promethazine (Phenergan)	25.†
Parsidol	25.
Diphenhydramine hydrochloride	25.
plus hyoscine hydrobromide	0.35
(Trimeton)	25.
plus hyoscine hydrochloride	0.35
Pyrathiazine (Pyrrolazote) hydrochloride	50.

* Effective in seasickness when given once a day.

† Effective in seasickness when given twice a day.

have been of especial interest in this connection. Apparently, promethazine (Phenergan, Lergigan) was first used by Beaumont in 1949[44] in conjunction with pyranisamine (Anthisan) maleate in a suppository. Although the favorable results obtained were attributed to Anthisan, there can be little doubt that Phenergan deserves most of the credit. In 1950, Ambrus and Ambrus[48] reported that Phenergan gave good results in almost every case tried. Unfortunately, no data were shown, so that the extent of this series remains unknown. The activity of this compound has been demonstrated repeatedly during the past few years.[10, 14–16, 47–51] Glaser and Hervey found 25 mg. of Phenergan to be superior to Benadryl but less effective than 1.0 mg. of hyoscine.[10] In aircraft, also, 1.0 mg. of hyoscine was found superior.[52] Since Phenergan is slowly absorbed, adequate time may not have been allowed for maximum effectiveness.[53] In this connection is the long duration of action of Phenergan, so that medication twice daily was sufficient to protect against seasickness.

Related phenothiazine compounds, such as diethylamino isopropyl phenothiazine (Parsidol) hydrochloride, pyrathiazine (Pyrrolazote) hydrochloride, and thiazinimon (Multergan) methyl sulfate, have been found effective in seasickness[16] and Pyrrolazote in airsickness. The profound pharmacologic changes resulting from small chemical differences add interest to this group of compounds. Lisergan,[16] Diparcol,[16] and chlorpromazine (Thorazine)[7] are all ineffective. The failure of chlorpromazine to protect man against seasickness was somewhat surprising, for it had prevented swing sickness in dogs[6, 54] as well as protecting man against a variety of emetic stimuli.

Thus far, three members of the piperazine series of antihistamines have been tested, with good results. Cyclizine (Marezine) hydrochloride, chlorcyclizine (Perazil, Diparalene) hydrochloride, and meclizine (Bonamine, Postafene) hydrochloride have demonstrated their effectiveness against seasickness[7, 16, 46] and airsickness.[14, 47, 48, 55] The most striking characteristic of these compounds has been their long

duration of action. Bonamine, especially, has been outstanding in this regard, protecting for at least 24 hours. Given once daily it has been effective against seasickness,[16] and given 24 hours prior to take-off, it has protected against airsickness.[47, 48] Recently, a single dose (50 mg.) given at time of sailing significantly reduced the over-all incidence of sickness during a transatlantic crossing.[7]

Another antihistamine of different chemical structure that has proved its worth is prophenpyridamine (Trimeton) maleate. It was effective against both airsickness[47] and seasickness.[16]

The ability of both belladonna alkaloids and antihistamines to protect suggested that their combination might be even more effective. Chinn and Oberst[39] combined 50 mg. of Benadryl with 0.65 mg. of hyoscine and found a lower incidence of airsickness than with either component alone. Unfortunately, side effects were also increased, so that the advantage was lessened. Reducing each constituent to half (25 mg. of Benadryl, 0.35 mg. of hyoscine) gave approximately the same protection as the full dose of either alone, with a reduction of side effects.[14, 15, 52] Hyoscine has also been combined with Trimeton[16, 56] and with Phenergan.[51] The protection in these cases was not demonstrably greater than that of the hyoscine alone.

The most frequent side effect of the above-described drugs is sedation. To control this undesirable complication, central nervous stimulants, such as caffeine and amphetamine, have been added to the motion sickness medicaments. The available data are rather limited, but there is no indication that prophylaxis against seasickness[57] and airsickness[52] has been impaired by this inclusion.

The practical usefulness of these drugs is not determined solely by their effectiveness. The frequency and severity of side effects must be weighed against the protection afforded. In many situations it is vital that the drug not impair one's ability to perform his job. The dilemma about whether one should prescribe antimotion sickness drugs and risk side effects or refuse such medication and risk varying degrees of incapacitation from seasickness or airsickness can have no firm answer. In large doses, the various belladonna alkaloids have unquestioned and serious side effects. These include cycloplegia, cardiac acceleration, and a diminution of sweating and salivation. Centrally, disorientation may be produced, with excitement and possibly hallucinations, giving way to secondary depression. Single doses of hyoscine adequate to cause these symptoms would only be given accidentally. In the range ordinarily employed (0.65 mg. to 1.2 mg.) the most common complaint is dryness of mouth. A decrease in sweating may occur but this has not handicapped men working under extreme heat.[5] Accommodative or other visual disturbances were not apparent with usual doses, but did occur when more than 1.5 mg. were given.[55]

A more detailed account of the types, incidence, and significance of side effects evoked by hyoscine has been prepared by Glaser[59] and can be found elsewhere in this Symposium. Few reports are available on the influence of hyoscine on psychomotor performance or intelligence tests. No deterioration at ground level or at a simulated altitude of 18,000 feet could be detected by Smith and Hemingway after 0.5 mg. of hyoscine.[60] The most comprehensive studies on psychologic efficiency have undoubtedly been performed by Payne and his co-workers.[61, 62] Hyoscine alone showed

least disturbance of the drugs tested and a Benadryl-hyoscine mixture the most. These findings are critically discussed by Payne in this issue.[62]

Periodic administration of hyoscine or related drugs may cause more serious effects than do single doses. This was made strongly apparent in a field study in which 2 mg. of hyoscine aminoxide were given three times daily.[15] Within 24 to 36 hours, over one-half the recipients suffered from dry mouth and blurred vision, and one-quarter reported nightmares. Of the 96 subjects, 11 experienced hallucinations, including one rather manic case. After 24 to 36 hours, these alarming symptoms subsided and no harmful after effects resulted. Hyoscine (0.75 mg.) given three times daily produced, in 36 hours, a high incidence of dry mouth and blurred vision and a single case of auditory hallucination.[16] Glaser, although contending that fears of cumulative poisoning are unfounded, recommends 1.0 mg. of hyoscine be given for the original dose and 0.5 mg. three times daily thereafter.[64] Corey and Webster,[65] using somewhat smaller doses (0.65 mg. initially and 0.3 mg. every 6 hours), reported no untoward symptoms except sleepiness, dryness of mouth and throat, and decreased lachrymation. Marksmanship was somewhat impaired.

Among the antihistamines of value in motion sickness, sedation is by far the most common side effect. This has been reported for Benadryl, Dramamine, Trimeton, Phenergan, Perazil, and Parsidol.[66, 67] In fact, of all the antihistamines possessing antimotion sickness effect, only Multergan seems free of this complaint.[68] On the basis of preliminary studies, Bonamine and 1-dimethylamino 2-(2-benzyl-*p*-chloro) phenoxyethane hydrochloride (Lilly Prep. 01780) cause relatively little sedation.[68] Apart from sedation, the most common complaints are dry mouth, blurred vision, dizziness, and fatigue.

The mode of action of these drugs is still unknown. Many workers believe the primary action is upon the peripheral vestibular structures. Dramamine has been reported of value in the vertigo of labyrinthine fenestration[69] and for Menière's syndrome.[70] The otolith references can be abolished or weakened by large doses of Dramamine (25 to 70 mg./kg.), but still larger doses (80 mg./kg.) are necessary to abolish the semicircular canal reflexes.[71, 72] When this dose was administered to rabbits after unilateral labyrinthectomy, there was no evidence of vestibular disturbance. In man, 200 mg. of Dramamine orally had no effect on the duration of nystagmus or vertigo.[73, 74] Although postrotational nystagmus has been modified by Dramamine, de Wit[75] believes the effect to be central, since only the duration of response was altered and not the intensity of angular acceleration required to cause the nystagmus. Atropine acts in a similar manner.

The effectiveness of antiemetic drugs on various sites in the vestibular nerve tract and brain center is still largely unexplored. Stimulation of the eighth nerve caused a blood pressure drop which could be abolished by Lergigan.[76] Changes in the sensitivity of the chemoceptive emetic trigger zone in the medulla can be followed by alterations in the animal's threshold to apomorphine.[77] Destruction of this area confers immunity to motion sickness.[78] It would be expected, therefore, that drugs raising this threshold would afford protection against motion sickness. Many drugs, however, possess anti-motion sickness properties without apparently influencing

this area. The literature on this point is still controversial. Some authors maintain that the apomorphine threshold is raised by Benadryl, Dramamine, and related compounds,[79–81] whereas other investigators can detect no change in threshold with even larger doses of drug.[82, 83] When drugs were used in doses approximating those given clinically, only White and co-workers[84] claim Benadryl or Dramamine protects against apomorphine. All other attempts with these compounds used in moderate doses failed to alter the emetic response to apomorphine in cats[83] or dogs.[2, 82, 83, 85]

On the other hand, raising the apomorphine threshold in animals does not necessarily mean that the compound is effective in man. Thus, chlorpromazine protects dogs against apomorphine,[6, 58–59] but does not protect man against motion sickness.[7] This emphasizes again the hazards of relying too heavily upon animal studies in testing of motion sickness drugs.

The emetic center is the ultimate target for all afferent emetic volleys. Its sensitivity can be measured by the level of oral copper sulfate required to evoke vomiting. There is no convincing evidence that any antiemetics in the usual clinical doses will significantly raise this threshold. Tests with chlorpromazine,[59] Phenergan,[54] Dramamine,[55] etc. have had no effect on copper sulfate vomiting. Reports[90, 91] that various agents act by depressing the vomiting center remain unsubstantiated.

The role of higher centers in initiating vomiting must be considered. In this connection is the correlation between the effectiveness of preparations against motion sickness and against paralysis agitans, which is generally believed to be a disturbance of higher centers. The belladonna alkaloids, Benadryl,[92–94] Trimeton,[93] Artane,[95] and Phenergan,[92] have been effective against both disorders. The correlation is far from perfect, for in the doses employed Diparcol, Thephorin, and Decapryn (all with antiparkinsonism activity) exert no protection against motion sickness. Conversely, Lilly 01780 prevented seasickness but was of no value against Parkinson's disease.[7] The similarity deserves further investigation.

Perhaps the most striking common feature among the effective medicaments is the anticholinergic activity. With the possible exception of Bonamine,[96] all motion sickness prophylactics possess this property. The mere antagonism of acetylcholine, however, does not assure antimotion sickness effect. Many compounds with parasympatholytic effects were completely ineffective against motion sickness: Banthine,[16] Probanthine,[16] Buscopan,[16] and Prantal.[62] These compounds are all widely used antispasmodics, owing much of their popularity to their lack of central nervous symptoms.[97] This is a characteristic trait of quaternary ammonium compounds. These facts emphasize the importance of central rather than peripheral antagonism of acetylcholine as a guide to the selection of effective motion sickness preventives.

Ideally, motion sickness drugs should be effective without producing any other pharmacologic effects. They should not be toxic, habit-forming, or cause disagreeable symptoms. While the search continues for more effective drugs, remedies now are available that will decrease the incidence of motion sickness to about one-third without producing incapacitating side effects.

Table I lists drugs which have been shown to be effective in preventing seasickness when given in the dose indicated three times a day or less. All of these drugs have

shown to be effective in airsickness when a single dose of the drug was given prior to flight.

Both in military and civilian life, personnel may have had so little flying or sailing experience or participate so infrequently that adaptation does not occur. It is in this group that motion sickness drugs may be of greatest value. The use of drugs may be helpful, since there are indications that adaptation to motion may occur even while taking drugs.[98, 99] Thus, proper therapy may prevent establishment of the "habit" of motion sickness.

It should be borne in mind with all of these drugs that they are active pharmacologic agents and are capable of producing untoward effects when used in large quantities. The usual precautions with regard to the toxic effects of hyoscine and the antihistamines should be followed.

BIBLIOGRAPHY

1. Tyler, D. B., and Bard, P.: Motion sickness, Physiol. Rev. *29*:311, 1949.
2. Noble, R. L.: Medication prior to and during World War II, Internat. Rec. Med. & Gen. Pract. Clin., 1954.
3. Chinn, H. I., and Plotnikiff, N. P.: Evaluation of various techniques for screening antimotion sickness drugs, J. Appl. Physiol. *5*:392, 1953.
4. Noble, R. L.: Methods of assaying motion sickness preventatives on dogs, Canad. J. Res. *E23*:228, 1945.
5. Noble, R. L.: The effect of barbiturates and other substances on motion sickness in dogs, Canad. J. Res. *E26*:283, 1948.
6. Cook, L., and Toner, J. J.: The anti-emetic action of chlorpromazine, SKF No. 2601-A (RP-4560), J. Pharmacol. & Exper. Therap. *110*:12, 1954.
7. Handford, S. W.; Cone, T. E., Jr.; Chinn, H. I., and Smith, P. K.: Drugs preventing motion sickness at sea, J. Pharmacol. & Exper. Therap. *111*:447, 1954.
8. Hollino, H. E.; McArdle, B., and Trotter, W. R.: Prevention of seasickness by drugs, Lancet *1*:127, 1944.
9. Luyex, H. M. C.: Motion sickness preventives, Com. Aviation Med. Report 306, April 1944.
10. Glaser, E. M., and Hervey, G. R.: The prevention of seasickness with hyoscine (scopolamine), benadryl, and phenergan, Lancet 2:749, 1951.
11. Hollino, H. E.: Travel sickness, Pharm. J. *112*:139, 1951.
12. Co Tui, and Debruille, C.: The comparative toxicity and effectiveness of scopolamine hydrobromide ($C_{17}H_{21}O_4N.HBr$) and scopolamine aminoxide hydrobromide ($C_{17}H_{21}O_5N.HBr$), Am. J. Pharm. *117*:319, 1945.
13. Chinn, H. I.; Strickland, B. A.; Oberst, F. W.; Wilks, S. S., and Tinkham, M.: Evaluation of some drugs in motion sickness, J. Aviation Med. *21*:424, 1950.
14. Chinn, H. I.; Waltrip, O. H., and Massengale, H. W.: Further studies on the effectiveness of various drugs against airsickness, J. Aviation Med. *22*:535, 1951.
15. Chinn, H. I.; Handford, S. W.; Cone, T. E., Jr., and Smith, P. K.: The effectiveness of various drugs for the prophylaxis of seasickness, Am. J. Med. *12*:433, 1952.
16. Chinn, H. I.; Handford, S. W.; Smith, P. K.; Cone, T. E., Jr.; Redmond, R. F.; Maloney, J. V., and Smythe, C. M.: Evaluation of some drugs in seasickness, J. Pharmacol. & Exper. Therap. *108*:69, 1953.
17. Sellers, E. A.; Parker, J. M., and Stephenson, N. R.: Motion sickness experiment, Appendix F., Nat. Res. Council, Canada, Nov. 27, 1942.
18. Noble, R. L.: Motion sickness, Rept. to Assoc. Com. on Army Med. Res., 17th Oct., 1944.
19. McLaughlin, F. L.: Nembutal in seasickness, Canad. M. A. J. *32*:544, 1935.
20. Barrow, L. L.; Conn, H. F., and Williams, S. C.: A report of the comparative study of motion sickness remedies on troops at sea, Bull. Subcom. Motion Sickness, 55, 1943.

21. Smith, P. K.: Present status of drugs for use in motion sickness with particular reference to airsickness, Proj. No. 468, AAF Sch. Aviation Med. 14, June 1946c.
22. Noble, R. L.: Treatment of experimental motion sickness in humans, Canad. J. Res. *E24*:10, 1946.
23. Thuer, W.: Reisekrankheit, Erfahrungen mit Synopen (Geigy) bei Seekrankheit, Schweiz. med. Wchnschr. *82*:312, 1952.
24. Benkendorf, L.: Über die Behandlung der Seekrankheit, Deutsch. med. Wchnschr. *78*:393, 1953.
25. Voss, W.: Beitrag zur prophylaxe gegen Luftkrankheit, Medizinische. *1*:879, 1953.
26. Gay, L. N., and Carliner, P. E.: The prevention and treatment of motion sickness. I. Seasickness, Bull. Johns Hopkins Hosp. *84*:470, 1949.
27. Gay, L. N., and Carliner, P. E.: The prevention and treatment of motion sickness. I. Seasickness, Science *109*:359, 1949.
28. Rust, S. M., and Fosberry, F. M.: Prevention of seasickness, Brit. M. J. 2:98, 1949.
29. Shaw, C. C.: Dramamine trials in the United States Navy, Mil. Surg. *106*:441, 1950.
30. van Proosdij-Hartzema, E. G.: Dimenhydrinaat bij misselijkheid als symptoom van enige aandoeningen, Geneesk. gids *28*:41, 1950.
31. Gay, L. N.: A subsequent report on dramamine. The prophylactic and therapeutic control of motion sickness and vestibular disturbances, Mil. Surg. *108*:324, 1951.
32. Santesson, G.: Amosyt en nyctt sjösygmedel, Svenska Lakartidn *46*:2492, 1949.
33. Adams, S. C. L.: Dramamine and seasickness, Brit. M. J. 2:947, 1950.
34. Palmer, J. M.: Dramamine and seasickness, Brit. M. J. 2:946, 1950.
35. Christiansen, M.: Smo erfaringer om søsyge, Ugesk. f. laeger *112*:86, 1950.
36. Chinn, H. I.; Noell, W. K., and Smith, P. K.: Prophylaxis of motion sickness, Arch. Int. Med. *86*:810, 1950.
37. Strickland, B. S., Jr., and Hahn, G. L.: The effectiveness of dramamine in the prevention of airsickness, Science *109*:359, 1949.
38. Strickland, B. A., Jr.; Hahn, G. L., and Adler, H.: Studies on airsickness, J. Aviation Med. 22:137, 1951.
39. Chinn, H. I., and Oberst, F. W.: Effectiveness of various drugs in prevention of airsickness, Proc. Soc. Exper. Biol. & Med. 73:218, 1950.
40. Simon, S. W., and Seyler, L. E.: Dramamine in pilots, J. Aviation Med. *371*:1949.
41. Maycock, R., and Morant, G. M.: Trials of dramamine as a preventive for airsickness, Brit. Fly. Pers. Res. Comm. (Memo 20), February 1951.
42. Nickerson, M.: Dramamine, Science *111*:312, 1950.
43. Wright, W. L.: Effectiveness of newer drugs in seasickness, U. S. Armed Forces M. J. *1*:570, 1950.
44. Beaumont, F. K.: Antihistaminic drugs and seasickness, Brit. M. J. 2:1472, 1949.
45. Lozano de Lamo, E.: Tratamiento antihistamin del mareo, Medicinia Clinica *16*:276, 1951.
46. Ambrus, J. L., and Ambrus, C. M.: Motion-sickness and antihistamines, Lancet *1*:326, 1950.
47. Chinn, H. I.; Gammon, W. R., and Frantz, M. E.: Prevention of airsickness among airborne troops, J. Appl. Physiol. *5*:599, 1953.
48. Chinn, H. I.; Milch, L. J., and Dugi, A. J.: Comparison of various drugs against airsickness, J. Appl. Physiol. *6*:257, 1953.
49. Enoquist, S.: Et nytt svenskt sjoskjukemedel, Svenska Lakartidnigen *47*:1464, 1950.
50. Harper, J.: Prevention and treatment of travel sickness with promethazine chlorotheophyllinate, Lancet *1*:1141, 1951.
51. Glaser, E. M., and Hervey, G. R.: Further experiments on the prevention of motion sickness, Lancet *1*:490, 1952.
52. Chinn, H. I.; Strickland, B. A., Jr.; Waltrip, O. H., and McGeary, J. D.: Prevention of airsickness during training flights, U. S. Armed Forces M. J. *4*:1609, 1953.
53. Bethell, M. F.: Prevention of seasickness with hyoscine, benadryl, and Phenergan, Lancet 2:888, 1951.
54. Chinn, H. I., and Sheldon, G. L.: Unpublished data.
55. Evard, E.: Prévention et traitement du mal de l'air pas un nouvel anti histaminique; premiers résultats expérimentaux, Brux. Med. 33:173, 1953.
56. MacKay, E. M.: Stanford M. Bull. 1954. In press.

57. Gulli, O.: Reisesyke og dens behandling, Tidsskr. f. d. norske laegefor. *71*:762, 1951.
58. Keil, F. C.: The effect of oral doses of hyoscine (scopolamine) on visual efficiency, AAF Sch. Aviation Med. Res. Report 157 (1), 2 June 1943.
59. Glaser, E. M.: Side effects of motion sickness drugs, Internat. Rec. Med. & Gen. Pract. Clin., 1954.
60. Smith, P. K., and Hemingway, A.: Effect of hyoscine (scopolamine) on swing sickness and on performance, AAF Sch. Aviation Med. Res. Report III (1), 1943.
61. Payne, R. B., and Hauty, G. T.: The effect of motion sickness preventives upon certain perceptual motor components of the pilots' task, USAF Sch. Aviation Med. Proj. 21-1601-0004, Report 3, May 1953.
62. Payne, R. B.; Osier, D. R., and Tomlinson, P. A. S.: The effects of certain motion sickness preventives upon navigator proficiency, USAF Sch. Aviation Med. Proj. 21-1601-0004, Rept. 1, May 1953.
63. Payne, R. B.: Internat. Rec. Med. & Gen. Pract. Clin., 1954.
64. Glaser, E. M.: Experiments on the side effects of drugs, Brit. J. Pharmacol. *8*:187, 1953.
65. Corey, E. L., and Webster, A. P.: Effects of scopolamine on marksmanship, Com. Aviation Med. Report No. 268, Nat. Research Council, Nov. 1, 1943.
66. Norll, W. K.; Chinn, H. I., and Haberer, C. E.: Unpublished data.
67. Feinberg, S. M.; Malkiel, S., and Feinberg, A. R.: The antihistamines—their clinical application, Chicago: The Year Book Publishers, 1950.
68. Gay, L. N.: Prophylactic and therapeutic control of vestibular disturbances with dimenhydrinate, J. A. M. A. *145*:712, 1951.
69. Campbell, E. H.: The effectiveness of dramamine in relieving the vestibular reactions following the labyrinthine fenestration operation, Laryngoscope *59*:1261, 1949.
70. Anon.: Menière's syndrome. Queries and minor notes, J. A. M. A. *141*:500, 1949.
71. Fermin, H.; van Deinse, J. B., and Hammelburg, E.: De Werking van dimenhydrinaat op het labyrinth, Nederl. Tij. Geneesk *94*:3036, 1950.
72. Fermin, H.; van Deinse, J. B., and Hammelburg, E.: The effect of dimenhydrinate upon the labyrinth (an experimental study), Acta Otolaryng. *38*:513, 1950.
73. Bornninghaus, H. G.: Die Beeinflussung des experimentell ausgelösten Nystagmus und Schwindels durch Vomex A. Ztschr. Laryng. Rhin. Otol. *31*:558, 1953.
74. Witzeman, L. A.: A new treatment for vertigo, Eye, Ear, Nose, and Throat Monthly *28*:272, 1949.
75. de Wit, G.: Seasickness (motion sickness), a labyrinthological study, Acta oto-Laryng. Suppl. *108*:1, 1953.
76. Gernandt, B. E., and Schmiterlöw, C. G.: Some observations concerning the mode of action of the antihistamine drug "Lergigan" (N-alpha-methyl-beta-dimethylaminoethyl) phenothiazine hydrochloride in motion sickness, Brit. J. Pharmacol. *8*:181, 1953.
77. Wang, S. C., and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate, and cardiac glycosides, Gastroenterology *22*:1, 1952.
78. Wang, S. C., and Chinn, H. I.: Experimental motion sickness in dogs. Functional importance of chemoceptive emetic trigger zone, Am. J. Physiol. *178*:111, 1954.
79. Mitchell, L.: Dimenhydrinate vs. diphenhydramine, Science *112*:154, 1950.
80. Gorthe, H.: Experimentelle and klinische Therapie mit dimethylathulbenzhydril äther-1, 3 dimethyl 8 chlorxanthin (Vomex A), Die medizinische, 1953 (in press).
81. Ducrot, R., and Ducrot, P.: Etude comparative de l'action anti-émétique de quelques antihistaminiques de synthèse, Compt. rend. Soc. Biol. *145*:356, 1951.
82. Schmidt, C. D.; Sata, E.; Brizer, K. R., and Borison, H. C.: The effects of dimenhydrinate (Dramamine) and diphenhydramine (Benadryl) on apomorphine-induced emesis, J. Pharmacol. & Exper. Therap. *106*:412, 1952.
83. Boyd, E. M., and Boyd, C. E.: Antihistamines and apomorphine-induced vomiting, Canad. J. M. Sc. *31*:320, 1953.
84. White, J. M.; Freedman, D.; McCawley, E. L., and Gray, W. D.: Effect of certain dialkyl-substituted amino alkyl bearing compounds on apomorphine-induced emesis, Federation Proc. *9*:325, 1950.
85. Moser, C. E.; Harrisson, J. W. E.; Ambrus, J. L., and Leonard, C. A.: A note on the effect of antihistamine drugs on experimental vomiting, J. Am. Pharm. A. *40*:115, 1951.

86. Brand, E. D.; Harris, T. E.; Borison, H. L., and Goodman, L. S.: The antiemetic activity of 10-(alpha-dimethylaminopropyl)-2-chlorophenothiazine (chlorpromazine) in dog and cat, J. Pharmacol. & Exper. Therap. *110*:86, 1954.
87. Courvoisier, R.; Fournel, J.; Ducrot, R.; Kolsky, M., and Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3-(dimethyl amino-3-propyl)-10 phenothiazine (4,560 R.P.). Étude expérimentale d'un nouveau corps utilisé dans l'anésthésie potentialisée et dans l'hibernation artificielle, Arch. int. pharmacodyn. *92*:305, 1952.
88. Boyd, E. M.; Casrell, W. A., and Boyd, C. E.: Prevention of apomorphine-induced vomiting by (dimethylamino-1-n-propyl-3)-N-(2-chloro)-phenothiazine hydrochloride, Federation Proc. *12*:303, 1953.
89. Glaviano, V. V., and Wang, S. C.: Dual mechanism of antiemetic action of chlorpromazine, Federation Proc. *13*:358, 1954.
90. Rubin, A., and Metz-Rubin, H.: Effect of dramamine upon postoperative nausea and vomiting, Surg., Gynec. & Obstet. *92*:415, 1951.
91. Bénitté, A. C.: Le mal des transports, Bull. internat. Serv. Santé *25*:235, 1952.
92. Budentz, J.: The use of benadryl in Parkinson's disease, New England J. Med. *238*:874, 1948.
93. Gair, D. S., and Ducey, J.: Chemical structure of substances effective in treatment of parkinsonism, Arch. Int. Med. *85*:284, 1950.
94. Ryan, G. M. S., and Wood, J. S.: Benadryl in the treatment of parkinsonism: results in forty cases, Lancet *1*:258, 1949.
95. Schwab, R. S., and Tillman, W. R.: Artane in the treatment of Parkinson's disease, New England J. Med. *241*:483, 1949.
96. P'an, S. W.: Personal communication.
97. Anon.: Parasympathetic depressants—anticholinergic agents, Research Today *10*:31, 1954.
98. Lilienthal, J. L.: The effect of hyoscine on airsickness, J. Aviation Med. *16*:59, 1945.
99. Parker, J. M.; Fields, W. S.; Sellers, E. A., and Birt, C. H.: Report on sea trials with RCN experimental seasickness Remedy No. 1, RCN Med. Res. Unit, 1943.

Side Effects of Remedies for Motion Sickness

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When drugs are chosen to treat motion sickness, one of the most important considerations is the presence or absence of undesirable side effects (which may be taken in this context to mean all symptoms other than vomiting and nausea). For example, when dimenhydrinate (Dramamine) was introduced, it was claimed to be a suitable drug for motion sickness because it gave rise to few side effects.[1] Using the closely related compound diphenhydramine (Benadryl) few side effects were observed in controlled experiments,[2, 3] but the problem is complicated by a number of circumstances. While people are being exposed to motion, the effects of motion and the effects of drugs cannot be separated,[2] and patients who feel unwell sometimes blame the sea and sometimes the drug they have taken. Even people who are given a placebo at sea may complain that the pill, not the sea, has made them sick.[4] Although psychologic influences do not cause motion sickness very often,[5] there is much evidence that psychologic influences can cure motion sickness,[6] and it is particularly important to exclude bias if side effects are to be properly assessed.

In experiments conducted at sea or in the air, it is usually observed that drugs that prevent motion sickness give rise to few side effects.[2, 4, 7–10] In the absence of motion, however, drugs that best prevent motion sickness give rise to the most unpleasant effects.[2, 11] The problem is further complicated because the symptoms that arise after taking drugs are not always due to the drugs alone, but may be due to questionnaires that were issued to collect data about symptoms.[2, 12, 13] In the past there has been no experimental work on this, but it has been shown recently that pharmacologic actions can be separated in man from the effects of motion and from psychologic influences. The present paper is an attempt to describe how such separate investigations can be carried out, and to review the knowledge that is now available.

EXPERIMENTAL TECHNICS IN THE ASSESSMENT OF SIDE EFFECTS

Single Doses

In a recent article by Gaddum,[14] it was emphasized that the actions of drugs should always be tested with simultaneous controls and also by the "double-blind" method, which means that indistinguishable drugs and placebos are issued by a code, so that neither those receiving drugs nor those assessing the results should know who are the controls or which drug was given to what subject. It may be added that, in experiments concerning remedies for motion sickness, especially concerning side effects, complete "crossing-over" is also desirable, so that each subject gets in turn each drug and an indistinguishable dummy substance, while the order in which these

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substances are given varies in different subjects. This combines all the advantages of simultaneous controls and of using the subjects as their own controls. The results can then be objectively assessed, because the action of each drug is compared, on the same people, with every other drug and with a placebo. That it is necessary to do this was shown by Glaser and Whittow,[13] who found that volunteer subjects reported more symptoms if placebos were given a few days after a drug of similar appearance than if placebos were given without previous medication. This means that if a drug is tested, the response obtained will depend not only on the actions of that drug but on previous experiences with similar tablets, capsules, or pills. It is important, therefore, to carry out experiments on a sufficiently large number of subjects to allow giving every possible sequence of drugs and placebos.

A comparatively simple method, which conforms to all these requirements, is available for testing side effects of drugs.[2] It was developed from a technic used in the assessment of preventives for motion sickness,[3, 9] and it has been used with minor modifications to assess the side actions of several remedies.[11, 15] Volunteers are given indistinguishable tablets (or pills, or capsules) on the "double-blind" and "crossed-over" principles (see above), and the tablets are issued in envelopes marked with the subject's name and the date, so that the subjects do not know whether they are receiving the same drug on each occasion or if they are all receiving the same drug. To make sure that the effects of any previous medication have worn off before another substance is given, the experiments are carried out at intervals of at least 48 hours. Tests are carried out at the same time of the day, because the incidence of symptoms can vary significantly at different parts of the day, and even between the beginning and the end of a lecture to medical students.[12]

The symptoms are assessed by means of questionnaires, which consist of simple questions in random order. Possible replies are also given in random order, and the subjects are asked to underline the correct answers. Some of the questions are worded in such a way that the presence of symptoms requires a negative answer, as for example: "Can you think as clearly as usual?" All this prevents the subjects from underlining every "yes" or every "no" without thinking about the questions and answers, and the risk of such lack of thought is further lessened by printing at random some alternative answers to the questions, for example "a little," in addition to "yes" or "no." There is not much to be gained from evaluating separately such answers as "a little," since the subjects' own grading of their symptoms must be highly subjective and liable to a number of errors, so that "a little" and "very" may both be taken as "yes."[12] The questionnaires include a blank space for comments by the subjects. Questions such as "What do you think are the effects of the drug you have taken?" are included in order to encourage further comments. A sample questionnaire was shown in a previous paper.[12]

It is difficult to say at what time intervals after taking the drugs the questionnaires should be answered, unless it is known in advance whether the drugs concerned are quick- or slow-acting. In an experiment with three common remedies for motion sickness, which included both quick- and slow-acting drugs, side effects after one and a half hours and after three hours did not differ significantly,[2] and it appears that any time between one and a half and three hours would give a reasonable comparison

in most instances. A further and simpler questionnaire can be given after a number of hours to assess late effects.[2] The results, including statistical comparisons between the effects of different substances, are worked out by a code before any of the experimenters know which subject had taken what substance on any given occasion.

Continued Administration

A method for testing side effects during continued administration of drugs was also devised.[2] The "double-blind" method still applies, and tablets (or pills, or capsules) are again issued in labeled envelopes, but "crossing-over" has to be done by a different scheme, and the questionnaires are given out at least twice daily. The number of tablets to be issued to every subject on every day of the experiment depends on the drug that is to be given most frequently. Thus, if one drug has to be given three times daily and the others twice or once daily, then every subject must get a tablet three times daily during the whole experiment, placebos being supplied at times when medication is not required.

Before issuing any drugs it is necessary to give placebos to every subject for at least one day, but it might be better to do so for three days, owing to habituation (see below). It is interesting to note, for example, that in one experiment a volunteer subject withdrew on the first day because he thought the "drug" was too unpleasant, but he had taken only lactose tablets.[2] After the initial period each drug is given to an equal proportion of subjects for an equal number of days. Then placebos are again given for at least two days, but preferably for three days. The medication is changed over and continued for as many days as before, and the process is repeated until each subject has taken every drug. This means that there must be as many experimental periods as there are drugs, and that between each experimental period, placebos must be given for two or three days. Of course, each drug must be given to the same number of subjects during each experimental period. Thus, again, "crossing-over" is achieved and accidental effects will be canceled out. The "double-blind" method still applies, and the experimenters assess the drugs by a code, but they may have to know which were the preliminary and intermediate periods during which placebos were being taken by the subjects. If it is desirable to make "blind" comparisons, not only between drugs but also between drugs and placebos, one set of placebos can be provided for initial and intermediate periods, and further indistinguishable dummies can be included among the coded pills, tablets, or capsules.

EFFECTS OF QUESTIONNAIRES

One of the most striking findings in a recent experiment concerned with side actions of drugs was the high incidence of symptoms recorded by people who were given questionnaires to answer but who had taken no drugs or placebos.[2] It has now been shown that if any sample of the healthy population is given a printed form containing simple questions about symptoms of ill health, 63 to 94 per cent of the subjects will record at least one symptom, such as headache, drowsiness, giddiness, or dryness of the mouth. A series of tests was conducted on Asian students in Singapore,[2, 11, 13] British troops stationed in Singapore,[2] British students in Britain,[13]

and a highly educated and mature sample of the academic population of a university,[12] and both sexes were represented among the subjects, but the results were so uniform that errors inherent in the samples, or due to race or climate, could not have caused the responses.

There is not much evidence about the reasons for these symptoms. They cannot be entirely explained by "yes-proneness" because some of the questions were so worded that the presence of symptoms required a negative answer, and because symptoms were frequently recorded about which no questions had been asked. The most probable explanation is that the very care with which the questionnaires were devised made people notice or imagine symptoms of which they would otherwise have been unaware.[2, 12] Whatever the reason, the high incidence of symptoms among subjects who have received no treatment must be taken into consideration when experiments are being designed.

EFFECTS OF PLACEBOS

Although placebos can cause symptoms,[2, 4] they do not significantly alter the incidence of seasickness in experiments on large samples.[6] When people who were not exposed to motion were given placebos but no questionnaires about symptoms, only about 7 per cent of the subjects reported symptoms,[12] and some of these may have had some underlying minor illness. When people were given both placebos and questionnaires, they did not record more symptoms than when they were given questionnaires alone.[2, 12] This shows that placebos neither cause nor prevent symptoms to a significant extent, and it might be asked why they should be given at all. But only placebos can prevent the subjects and the investigators from knowing when control tests are being carried out,[12] and for this reason they must remain an important part of any experiment on the actions (especially the side actions) of drugs.

HABITUATION

The term "habituation" means a lessening of responses to any repeated stimulus. It may also mean a gradual lessening of the effects of drugs, and it is frequently used in the latter sense. Experiments have shown that habituation to the side actions of motion sickness remedies does take place.[2] This was particularly marked with regard to promethazine hydrochloride (Phenergan), which has the same action as promethazine-8-chlorotheophyllinate (Avomine). If hyoscine (scopolamine) hydrobromide was given for four days running in initial doses of 1 mg., followed by 0.5 mg. three times daily, there was also a diminution of symptoms, but the incidence of blurred vision did not diminish. Whether blurred vision would always persist after several days, or whether this was a chance finding in a sample of moderate size, cannot be stated conclusively from the available evidence. What can be said is that there need be no serious fear of cumulative poisoning by remedies for motion sickness.[2] Of course, every drug can be unusually toxic to some people, and it may be preferable to change over to another drug if undesirable effects are present,[16] rather than to rely on habituation to eliminate these effects.

Another important aspect of habituation is that repetition of a stimulus, such as

TABLE I

Effects of Drugs in the Presence of Sea Motion and on Land
Compiled from data given by Glaser and Harvey[3] and Glaser[2]

Symptoms Recorded by Subjects	Proportion of Subjects Recording Symptom, in %							
	Hyoscine (scopolamine) hydrobromide 1 mg.		Promethazine hydrochloride (Phenergan) 25 mg.*		Diphenhydramine hydrochloride (Benadryl) 25 mg.†		Indistinguishable Placebo	
	At sea	On land	At sea	On land	At sea	On land	At sea	On land
Drowsiness	49	82	46	70	43	57	44	28
Headache	30	44	32	30	38	16	52	20
Giddiness	24	52	15	16	18	10	34	4
Dryness of mouth	87	92	58	28	54	20	44	18
Protection from vomiting	94	—	61	—	44	—	—	—
Preferences expressed by subjects	37	—	29	—	23	—	11	—
Considered unpleasant	—	66	—	34	—	21	—	8
Numbers taking substance	68	50	65	50	68	49	68	50

* Corresponds to about 50 mg. of promethazine-8-chlorotheophyllinate (Avomine).
† Corresponds to about 50 mg. of diphenhydramine-8-chlorotheophyllinate (Dramamine).

the simple procedures of an experiment in clinical pharmacology, will in itself cause a significant diminution of responses, so that people who are repeatedly given questionnaires will record progressively fewer symptoms.[2, 12, 13, 17] Such habituation is most marked in short experiments, and once habituation is established, there is no further significant decrease of symptoms.[11, 13] Of course, if experiments are "crossed-over," habituation need not affect the results. If experiments are not "crossed-over," they may become meaningless under certain conditions, owing to the impossibility of assessing whether changes are caused by differences in drugs or by habituation to the experiment as such.

EXPERIMENTAL OBSERVATIONS OF SIDE ACTIONS

It is clear from the foregoing that isolated observations of side actions can be misleading, and it is known that individual hypersensitivities exist to every drug. Chinn and his colleagues[18] described a case of acute mania after several doses of 0.75 mg. of hyoscine hydrobromide, but the present author has now given large single doses of hyoscine (1 mg.) more than 400 times[2, 3, 9, 13, 17] and continued treatment with large doses of hyoscine 32 times,[2, 19] without serious ill effects. Further, the literature contains well over a thousand cases in which single doses of 0.6 to 1.2 mg. were given without serious ill effects.[4, 5, 10, 11, 20, 21] On the other hand, it is generally accepted that Dramamine causes few side effects, but some patients are ill

even after taking that drug, and fatal cases have been reported.[22] On one occasion the present author became drowsy and almost disoriented after taking 50 mg. of chlorpromazine (Largactil), but in an objective experiment on a large sample this drug was found to have few side effects.[15]

Experimental observations of side effects are summarized in the table. The experiments at sea[2] and those on land[7] were carried out at different times and with different subjects, but the experimental plan was the same both times, and it was sufficiently stringent to exclude the errors discussed above, so it is believed that the results of the two experiments may be safely compared.

In experiments at sea, 44 per cent of subjects receiving a dummy complained of drowsiness, 52 per cent of headache, 34 per cent of giddiness, and 44 per cent of dryness of the mouth. In strictly comparable experiments on land, 28 per cent complained of drowsiness, 20 per cent of headache, 4 per cent of giddiness and 18 per cent of dryness of the mouth, when they were given dummies. This shows that symptoms commonly described as side effects were more frequent among untreated people at sea than on land, and that some of the drowsiness, headache, giddiness, and dryness of the mouth experienced at sea was caused by sea motion.

In the presence of sea motion, hyoscine hydrobromide in doses of 1 mg. caused drowsiness in 49 per cent, headache in 30 per cent, and giddiness in 24 per cent of subjects. On land, in an identical experiment, the same amount of hyoscine caused drowsiness in 82 per cent, headache in 44 per cent and giddiness in 52 per cent of subjects. Dryness of the mouth was present in 92 per cent of the subjects on land and in 87 per cent of the subjects at sea. This shows that, apart from dryness of the mouth, fewer people feel unwell after hyoscine hydrobromide at sea than on land.

The results are very similar with regard to the histamine antagonists Phenergan and Benadryl. On short trips these drugs prevent motion sickness less effectively than hyoscine,[2, 8–10] and on land they have fewer side effects than hyoscine,[2] but the proportion of people who were drowsy after Phenergan and Benadryl was still greater on land than at sea. On land all the drugs were followed by much more drowsiness than the dummy, and some of them also by more headaches and giddiness. At sea, taking the drugs was followed by fewer headaches and less giddiness than taking the dummy, but drowsiness was about equally frequent every time.

An important aspect of side effects is the preference expressed by those taking the drugs (see table). Here again, the difference is very striking between responses at sea and on land. At sea the subjects' own preferences for drugs conformed precisely with objective assessments of the preventive action against motion sickness. On dry land the subjects' preferences were the reverse, and drugs that were preferred at sea were considered the most unpleasant on land.

When drugs were given for periods of four days the incidence of side effects was again inversely proportional to the action against motion sickness,[2] and, as has been said above, habituation took place.

The results summarized in the table have been repeatedly confirmed. Using a similar experimental plan, Chinn, Milch, and Dugi[9] obtained results during flight that conform to those given here. Using a different dosage, Chinn and his colleagues[7]

observed more side effects at sea in subjects who had taken ineffective drugs or dummies than in subjects who had taken hyoscine and Benadryl. Payne[21] observed less psychologic efficiency during flight in subjects who had taken Benadryl than in subjects who had taken hyoscine, and less efficiency may be taken to mean the same thing as more side effects. The side effects observed on land after taking hyoscine, Phenergan, Benadryl and a dummy[2] have been confirmed under identical conditions by Whittow.[11]

Several conclusions can be drawn from this. It has already been said that a patient who is exposed to motion and who is receiving treatment against motion sickness is, in fact, experiencing a combination of the effects of the motion and the drug. It is obvious also that there is an inverse proportion between the protection against motion sickness afforded by a drug at sea or in the air and the ill effects of the same drug on dry land. At a glance this may seem difficult to understand, but it conforms with one of the theories of drug actions in motion sickness. It was suggested by Holling[23] that hyoscine does not depress the vomiting center or its afferent paths but that it suppresses discordant impulses arising in the labyrinths and muscles and joints. It was also suggested by Burn[24] and Glaser[2] that all seasickness remedies owe their effects to a common hyoscine-like central action. Thus, if discordant impulses converge on the central nervous system in the presence of irregular motion, they give rise to vomiting, nausea, and other effects, and the action of hyoscine will be to suppress these impulses. If discordant impulses are not present, hyoscine gives rise to disturbances. Other seasickness remedies presumably do the same.

Apart from central actions, hyoscine also has atropine-like peripheral actions, of which dryness of the mouth and flushing of the face are the most important.[2, 11, 13] Other drugs that prevent motion sickness do not give rise to significantly more dryness of the mouth and flushing of the face in single or repeated doses than dummy tablets,[2, 11] although in the air Phenergan was found to suppress sweating.[5] This makes it appear probable that an atropine-like peripheral action plays little or no part in the prevention of motion sickness, which conforms with observations by Holling, McArdle, and Trotter.[20] If this is true, it may be said that the ideal drug should have a marked hyoscine-like action but no atropine-like action. Experiments suggest that *p*-chlorobenzhydryl-*m*-methylbenzylpiperazine (Postafene) has these advantages, and also a long-lasting action, although it is less effective in single doses than hyoscine.[5]

SELECTION OF SUITABLE REMEDIES

A study of side effects may provide a clue to the selection of motion sickness remedies. When experiments on side effects of motion sickness remedies were first planned, it was thought that knowledge of side effects would help to exclude undesirable remedies, but the findings suggested that some side effects on dry land were, in fact, evidence of value in the presence of sea motion.[2] It was then attempted by Whittow[11] to study side effects in order to select, not to eliminate, suitable substances, on the assumption that a hyoscine-like central action would suggest a preventive action against motion sickness.

A certain amount of caution is, of course, needed until more evidence is available. The suggestion that motion sickness remedies may owe their effects to an antiacetylcholine action[7, 15] is compatible with the views expressed here, because any substance that interferes with cholinergic fibers would naturally depress the central nervous system. There are, however, specific centers and pathways of vomiting in the brain,[25] and there is at least a theoretical possibility that some remedy might inhibit the pathways or centers of vomiting without giving rise to any hyoscine-like central action.

CONCLUSIONS AND SUMMARY

Side actions must be assessed in experiments designed to exclude all possibility of bias and all accidental influences. This is best achieved by "crossed-over" and "double-blind" experiments in which all procedures are carefully controlled. Isolated observations of side actions are meaningless, apart from showing up individual variations of responses.

Drugs that prevent motion sickness best have a hyoscine-like central nervous action on dry land. In the presence of motion, however, people who have taken such drugs have fewer side effects than people who have taken placebos. A hyoscine-like central action may, therefore, be evidence that a drug is effective against motion sickness. Some drugs that prevent motion sickness have an atropine-like peripheral action, but an atropine-like action is not a necessary attribute of preventives or remedies for motion sickness. Motion sickness in untreated people may also be accompanied by atropine-like peripheral responses.

All the evidence suggests that side effects in people who are being treated for motion sickness may be caused by the motion, and that some such side effects are inhibited by drugs.

If drugs with a strong hyoscine-like central action have different effects in the presence of motion than on dry land, then it seems possible that during moderate motion, or in people who are partly adapted to motion, these drugs act as they do on dry land. This could explain some of the discrepancies in different experiments with remedies for motion sickness.

BIBLIOGRAPHY

1. Gay, L. N., and Carliner, P. E.: The prevention and treatment of motion sickness, Bull. Johns Hopk. Hosp. *84*:470, 1949.
2. Glaser, E. M.: Experiments on the side-effects of drugs, Brit. J. Pharmacol. *8*:187, 1953.
3. Glaser, E. M., and Hervey, G. R.: The prevention of seasickness with hyoscine, Benadryl and Phenergan, Lancet *2*:749, 1951.
4. Hill, I. G., and Gurst, A. I.: Prevention of seasickness in assault craft. A report of experiments under tropical conditions, Brit. M. J. *2*:6, 1945.
5. Tyler, D. B.: The influence of a placebo, body position and medication on motion sickness, Am. J. Physiol. *146*:458, 1946.
6. Annotation: Motion sickness, Brit. M. J. *2*:553, 1952.
7. Chinn, H. I.; Handford, S. W.; Cone, T. E., and Smith, P. K.: The effectiveness of various drugs for the prophylaxis of seasickness, Am. J. Med. *12*:433, 1952.

8. Chinn, H. I.; Milch, L. J., and Dugi, A. J.: Comparison of various drugs against airsickness, J. Appl. Physiol. *6*:257, 1953.
9. Glaser, E. M., and Hervey, G. R.: Further experiments on the prevention of motion sickness, Lancet *1*:490, 1952.
10. Strickland, B. A.; Hahn, G. L., and Adler, H.: Studies on airsickness, J. Aviation Med. *21*:90, 1950.
11. Whittow, G. C.: Selection of motion sickness remedies, Malayan Pharmac. J. 3:1954. In press.
12. Glaser, E. M.: Some errors in the use of questionnaires, Clin. Sc. *13*:1954. In press.
13. Glaser, E. M., and Whittow, G. C.: Experimental errors in clinical trials, Clin. Sc. *13*:199, 1954.
14. Gaddum, J. H.: Clinical pharmacology, Proc. Roy. Soc. Med. *47*:195, 1954.
15. Glaser, E. M., and Newling, P. S. B.: Side actions of chlorpromazine (Largactil). In preparation.
16. Glaser, E. M.: Entstehung und Behandlung der Seekrankheit, Deutsch. med. Wchnschr. *78*:392, 1953.
17. Glaser, E. M., and Whittow, G. C.: Evidence for a non-specific mechanism of habituation, J. Physiol., Camb. *122*:43P, 1953.
18. Chinn, H. I.; Noell, W. K., and Smith, P. K.: Prophylaxis of motion sickness. Evaluation of some drugs in seasickness, Arch. Int. Med. *86*:810, 1950.
19. Glaser, E. M.: Hyoscine in treatment of seasickness, Lancet 2:341, 1952.
20. Hollino, H. E.; McArdle, B., and Trotter, W. R.: Prevention of seasickness by drugs, Lancet *1*:127, 1944.
21. Payne, R. B.: The effects of drugs upon psychological efficiency, J. Aviation Med. *24*:523, 1953.
22. Wyngaarden, J. B., and Sievers, M. H.: The toxic effects of antihistaminic drugs, J. A. M. A. *145*:277, 1951.
23. Hollino, H. E.: Wartime investigations into sea- and airsickness, Brit. M. Bull. 5:46, 1947.
24. Burn, J. H.: Pharmacological action of antihistamine compounds, Brit. M. J. *2*:691, 1950.
25. Borison, H. L., and Wang, S. C.: Physiology and pharmacology of vomiting, Pharmacol. Rev. 5:193, 1953.

Some Effects of Motion Sickness Remedies Upon Psychologic Performance

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The development and use of various drugs has often been paralleled by a lively interest in their effects upon psychologic behavior. Until about 10 years ago this interest was confined largely to the more socially significant drugs, such as opium and its derivatives, the barbiturates, narcotics of the methane series, and central stimulants, such as caffeine and the amphetamines. Scientific studies of their effects upon psychophysiologic processes can be found summarized in several excellent reviews.[2, 6, 25, 29]

Although such drugs continue to be the occasional subject of investigation, the past 10 years have seen relatively more emphasis on the study of antihistaminic and anticholinergic preparations used, among other things, for the prophylaxis of motion sickness. This emphasis has been motivated largely by three general considerations. First, the pharmacologist has sought a rough, simple index of autonomic activity, which might promote better understanding of the drugs' prophylaxis mechanisms. Second, commercial air and surface transportation industries, realizing the potentialities of remedies for the relief of distress during turbulent travel, have had to be concerned with the incidence and intensity of such discomforting side reactions as drowsiness, dizziness, headache, blurred vision, and various anhydrotic manifestations. Finally, military aviation has had to weigh the potentialities of such drugs for the prevention of motion sickness, on the one hand, against the unknown risk of performance deficit due to peripheral and central impairment, on the other. Substantial research effort, therefore, has been expended upon a better understanding of this risk and upon the discovery and development of remedies offering maximal protection with minimal secondary effects. The purpose of this paper is to discuss certain methodologic problems inherent in the study of performance effects, to summarize the knowledge gained, and to suggest certain problems that can be explored profitably in the future.

METHODOLOGY

The interests to be served by scientific investigation may often influence the choice of methods, and these, in turn, place certain limitations upon what can be learned. One may find, for example, that conventional methods of appraising the side effects of motion sickness remedies, such as questionnaires, interviews, rating scales, checklists, and other modes of subjective observation, have served commercial transportation interests very well, for their principal concern is with the comfort of passengers. In fact, there may be no better, or no other, means of collecting the necessary information. Military aviation, on the other hand, is necessarily less interested in subjective reports of discomfort than in the question whether the remedies will impair the

abilities, skills, and motivation required for the performance of duty. The conventional methods of study, therefore, are not well suited to this type of problem because it is scarcely possible to deduce from subjective data even the most general behavioral consequences of drug use. There is neither a close nor a necessary relationship between how a person says he feels and how well he performs tasks.[21, 22] Rather, the type of task, the basic ability, the degree of training, the goals provided, and similar factors are vastly more important determinants of performance level than subjective dispositions and feeling tones. Despite such facts as these, the use of subjective methods in forecasting treatment effects has persisted, and loose inferences drawn from them about the effects of drugs upon performance are legion.

If one wishes to understand the effects of certain drugs upon the performance of some particular task, such as pilotry or navigation, there is no completely satisfactory substitute for the direct observation of behavior in a realistic setting. Various practical circumstances, however, may militate against the use of realistic criteria. In this event, one can take advantage of the fact that the abilities and skills which subserve the "real-life" task are, to a substantial degree, separately identifiable and individually measurable in simpler, synthetic situations. For example, a navigator must perform arithmetic computations with speed and accuracy in order to maintain knowledge of his position. In the absence of an actual navigation setting for a drug experiment, a suitable measure of this particular skill is the USAF Numerical Operations Test (CI702B), which has a satisfactory self-correlation (r_{ii} *circa* 0.80) and a substantial relationship to actual navigation proficiency (r_{xy} *circa* 0.40). Typically this test accounted for about 14 per cent of the aptitude index (stanine) used to select navigation students during World War II.[7] An experimental demonstration that drugs impair the speed and accuracy of performance on this test would give rise to some expectancy that the computational component of navigation skill would be impaired in actual flight, other things being equal. By the same token, such an expectancy might be entertained with respect to navigation proficiency in general if drug effects upon several relevant aptitude tests were demonstrated. Similar arguments can be advanced for the study of the effects of drugs upon test scores that represent perceptual-motor abilities involved in pilotry.[15] In general, then, synthetic tasks can serve as appropriate indicators of drug effects upon some ultimate task insofar as they are (a) reliable estimators of whatever they measure, and (b) correlated with the task to which the outcomes are to be extrapolated, other factors being equal. Conversely, for such purposes, there would be little point in studying an index (such as dry mouth) that is not likely to be related to ultimate task proficiency. The burden, therefore, is always on the investigator to show that he is using a criterion measure that is a reliable characteristic of the person measured and relevant to the ultimate purposes of the experiment.

Another methodologic consideration that arises whenever some ultimate task criterion (say, navigation) cannot be employed is the choice of what to measure. Since no single synthetic task can be regarded as thoroughly representative of the real task, it becomes necessary to sample what might be called the *spectrum* of abilities and skills relevant to the real task. By this means, one can not only learn something about the differential sensitivity of various psychologic processes to drug impairment,

but can also weight the various effects across this spectrum in accordance with the individual relevancies of the tests to the real task, thereby improving the possibility of applying judiciously a composite estimate of impairment. No one has yet attempted this weighting procedure, but data are available for its exploration.[16, 17]

Still another procedural problem arises from the consideration that drug effects upon aircrew performance occur not in a laboratory but in an aircraft at altitude under varying conditions of noise, vibration, anxiety, lowered oxygen tension, work prolongation, and motivation, to name a few. Certainly no final estimate of impairment in aircrew performance can be gained from studies using synthetic situations unless the interactions of drugs with these other factors are known. Much more, of course, could be said about methodologic problems peculiar to the study of drug effects upon aeronautic tasks by means of synthetic test situations, but the ones already mentioned probably constitute the main considerations. To say that the task is a formidable one is gross understatement.

The experimental findings to be discussed shortly are based upon criteria that vary widely in their reliability (duplicability) and in their relevance to aeronautic tasks. Nevertheless, in all cases they have at least the merit of having been obtained by relatively objective methods of measurement, and they reflect what a person can do under drug influences as contrasted with how he feels.

SCOPE OF INVESTIGATION

One goal of any literature review is the classification of information in as many ways as may be helpful to an investigator contemplating further work on the problem. Therefore it has seemed profitable to indicate the scope of the present literature in terms of the drugs used and the psychologic processes measured, without the complications and discontinuities arising from associated discussions of outcomes. The latter will be taken up later.

Drugs

With rare exceptions the drugs chosen for investigation have been those exhibiting anticholinergic and/or antihistaminic properties. Hyoscine hydrobromide alone, in doses ranging from 0.5 mg. to 1.5 mg., has perhaps been the most frequently tested,[4, 11–13, 15, 17, 19, 20, 22, 26, 28] and there are numerous instances in which it has been studied in mixture with other agents, such as diphenhydramine hydrochloride,[8–10, 15–24] hyoscyamine,[3, 27, 28] and dextroamphetamine.[8, 17] Diphenhydramine-8-chlorotheophyllinate in 100 mg. doses has been studied with considerably less frequency.[8, 11, 14, 15, 20, 30] Diphenhydramine hydrochloride alone in 50 mg. doses,[15, 20] and in combination with dextroamphetamine,[17] has been subjected to only limited study. *N* [dimethylamino methyl] ethylphenothiazine hydrochloride in 25 mg. doses,[17] meclizine in 50 mg. doses,[23] tripellenamine HCl in 100 mg. doses,[14] the so-called Army Motion Sickness Preventive,[27] and a mixture containing hyoscine, hyoscyamine, nicotinic acid, methyl benzedrine, and sodium barbital[3] round out the picture for all practical purposes. Many of these studies permit the comparison of two or

more preparations in terms of common criteria,[2, 5, 11, 14, 16, 17, 19, 20, 23, 24, 25] and several permit the comparison of two or more criteria in terms of common preparations.[2, 5, 11, 14, 16, 20, 23, 24, 27]

Criteria

Performances sampled under drug conditions range all the way from simple sensory and perceptual functions measured in the laboratory[5, 11, 12, 28] to complex navigation tasks carried on in aircraft at altitude.[13, 17] Between these extremes can be found a wide variety of synthetic tasks, which simulate certain components of pilotry and/or navigation to varying degrees. Some examples of these are numerical calculation,[14, 16, 20, 27] code substitution,[27] perceptual speed, spatial visualization and orientation, figure analogies, general reasoning, and verbal comprehension,[16] rote learning and retention,[23] and perceptual-motor coordination ranging from very simple compensatory and following pursuit[10, 16, 26, 27] to very complicated, multidimensional coordination.[8, 9, 14, 16, 18, 19, 20–22, 30] Steadiness,[26, 27] simple reaction time,[30] and marksmanship[4] have also been investigated. Recently several studies have attempted to discover the extent to which drug effects interact with the effects of other conditions, such as work prolongation,[8, 9, 18–20] task attitudes,[18, 21] motivation,[8, 9, 22, 23] information feedback systems,[8, 9, 22] and degree of training.[23] One study each has been devoted to the effects of drugs upon two-member team behavior[24] and upon the subject's estimation of future performance capability.[10]

SCOPE AND MAGNITUDE OF IMPAIRMENT

Sensory Functions

The available studies of sensory functions have been concerned primarily with vision. With respect to this modality and its accessory mechanisms, investigators are in general agreement that moderate doses of hyoscine hydrobromide (0.5 to 0.7 mg.) have no significant effects upon accommodation,[28] the visibility of charts, computers, and octants,[13] or the visual component of marksmanship,[4] although Keil has shown that oral doses greater than 1.5 mg. lowered visual efficiency (accommodation, near and distant vision) in about 50 per cent of the subjects tested.[12] The situation is much the same with respect to 100 mg. doses of diphenhydramine-8-chlorotheophyllinate (Dramamine). Katz and Wendt found no significant effects of this drug upon dial reading at near fixation, Landolt ring perception at far vision, or upon Orthorater performance at both near and far vision under varying levels of illumination.[11] Likewise, Faucett detected no significant effect of Dramamine upon visual acuity, color matching, stereoscopic vision, or the flicker fusion threshold.[5]

With respect to auditory functions, Faucett found no significant effects of Dramamine upon auditory acuity measured in a sound recognition trainer,[5] and Katz and Wendt found that neither hyoscine nor Dramamine affected audiometer thresholds for pure tones from 64 to 11,584 cycles.[11]

From these studies, therefore, it appears that neither hyoscine nor Dramamine in moderate doses is prejudicial to the functioning of the most important sensory modalities. The results have several implications worthy of note. First, they are in

some conflict with subjective results which reveal occasional instances of blurred vision. Unfortunately there are no studies that permit an estimate of the correlation between subjective reports and objective measurements of visual changes, but those available suggest that if noticeable blurring occurs it does not seem to be of sufficient magnitude to interfere with visual efficiency. Second, the studies suggest that any adverse effects that hyoscine and Dramamine may have upon so-called higher mental functions are due to central rather than peripheral impairment. Finally, the studies do not contraindicate the use of these remedies by persons engaged in flying duties.

Perceptual-Intellectual Functions

The classification of tasks in terms of the basic psychologic processes that subserve them is a complicated, and sometimes arbitrary, matter. There are, of course, factorial methods of analysis that permit rather precise identification of the constituents of any given constellation of behavior. For the present purposes, however, it will be sufficient to define perceptual-intellectual functions as cognitive processes that involve only minimal, simple, or nonspecific motoric adjustments. Some examples are the comprehension, learning, and retention of symbolic material, reasoning, imagery, and the recognition of spatial and other relationships among objects, symbols, and persons, to name a few. These and kindred processes can be measured with varying degrees of purity by paper and pencil tests,[7] although tests of psychomotor ability are seldom, if ever, completely devoid of them.[15] Extensive studies of the relevancies of such tests to navigation and pilotry have shown that the former task draws more heavily upon perceptual-intellectual processes while the latter draws more heavily upon perceptual-motor processes.[7, 15] Therefore the remarks of this section can be regarded as applying somewhat more to navigation than to pilotry.

We have already noted Lilienthal's findings that 0.6 mg. doses of hyoscine hydrobromide seemed not to affect the use of charts, computers, and octants.[13] This is consistent with the demonstration by Payne, Osier, and Tomlinson that 0.65 mg. doses of hyoscine induced no significant impairment in actual navigation proficiency displayed during map reading and dead reckoning missions.[17] The relatively benign effects of hyoscine in moderate doses were further demonstrated by Payne, Moore, and Bethurum,[16] who found significantly adverse effects in only 4 of 32 tests of intellectual and perceptual ability. These effects were confined to perceptual speed and spatial visualization functions, and the losses ranged from 8 to 10 per cent. On the other hand, hyoscine did induce a small, but statistically significant, deficit in the retention of a barely learned serial order verbal task.[22]

The effects of diphenhydramine-8-chlorotheophyllinate upon perceptual-intellectual functions are only slightly more profound. MacKay and Ferguson were unable to show significant deficit in calculation skill,[14] and the present author and his colleagues found that only 5 of 32 tasks were significantly impaired.[16] These deficits, ranging from 6 to 12 per cent, occurred in tests of spatial orientation, reasoning by analogy, simple algebraic computation, and reading information from printed dials.

In comparison with hyoscine and Dramamine, 50 mg. doses of diphenhydramine hydrochloride (Benadryl) increased not only the scope but also the depth of impair-

ment across the spectrum of abilities.[16] The only study available on this drug revealed significant deficits in 10 of 32 tests employed, and the losses ranged from 6 to 24 per cent. The processes affected were perceptual speed, spatial visualization and discrimination, the comprehension and covert manipulation of symbols, and the rapid handling of numerical information.

A combination of hyoscine (0.65 mg.) and Benadryl (50 mg.) produced more frequent and more profound deficits than a simple summation of their individual effects would suggest. Printed aptitude test methods revealed that 17 of 32 tests were adversely affected by this preparation.[16] The processes represented in these tests were perceptual speed, the comprehension and covert manipulation of symbolic material, the visualization and discrimination of spatial relationships and mechanical movements, and the rapid handling of numerical information gained from dials, graphs, and tables. The losses ranged from 6 to 18 per cent, but some two thirds of these were over 10 per cent. A comparison of Benadryl-hyoscine with hyoscine alone by aptitude test methods agrees closely with their comparison in terms of actual navigation proficiency,[17] although the relative loss in the navigation task was somewhat smaller for both preparations.

Several additional remedies have received only occasional study in terms of perceptual-intellectual processes. One study, for example, showed that 25 mg. doses of promethazine (Phenergan) significantly depreciated navigation proficiency.[17] Another revealed that 50 mg. doses of meclizine disturbed the retention of a serial order verbal task.[22] MacKay and Ferguson found some impairment of calculation ability with 100 mg. doses of tripellenamine HCl.[11] Finally, Smith has noted that the Army Motion Sickness Preventive (sodium amytal, hyoscine, and atropine) had a small but statistically negligible effect upon addition and code substitution.[27]

Although the foregoing information is far less than desired, there are two practical generalizations that seem well supported. First, it is apparent that various remedies differ significantly from one another both in the scope and depth of impairment they produce.[16, 20] Unfortunately, the more adverse drugs tend to be the ones that afford the better protection against motion sickness, but this may give some clue to their prophylactic mechanisms. Second, it is clear that hyoscine and Dramamine in moderate doses remain the drugs of choice as far as their effects upon intellectual and perceptual functions are concerned, although it should be noted that certain newer remedies (e.g., meclizine) have not yet been adequately tested.

Perceptual-Motor Functions

Tasks falling in this category are those in which proficiency depends to a high degree upon the speed and accuracy of motor adjustments, although they are not necessarily devoid of intellectual and perceptual components. Some examples are visuomotor reaction time, steadiness, various forms of following and compensatory pursuit, and, of course, pilotry.

We have already noted Corey's findings that 0.65 mg. doses of hyoscine had no significant adverse effects upon marksmanship, even when followed with 0.32 mg. doses every six hours.[4] This result implies a lack of motoric disturbance as well as

a lack of visual deficit, and upon this basis it agrees with Smith's negative results on a steadiness-aiming task.[26] Serial reaction tasks and pursuit tasks varying widely in difficulty and duration have likewise failed to reveal deficits attributable to hyoscine given alone in moderate doses.[16, 19, 20, 26] The effects of 100 mg. doses of Dramamine are comparable to those of hyoscine. Strickland, Hahn, and Adler observed no deleterious effects of Dramamine upon either simple visual reaction time or complex serial reaction.[20] MacKay and Ferguson[14] and Payne, Moore, and Bethurum[16] reported negative results on various tests of psychomotor coordination.

Benadryl alone in 50 mg. doses did not retard the learning of rotary pursuit, two-hand coordination, and complex serial reaction tasks.[16] A mixture of 0.65 mg. hyoscine with 50 mg. Benadryl likewise failed to retard the learning of rotary pursuit, two hand coordination, complex serial reaction, and mirror tracing tasks,[10, 16] but evidence will be presented later to show that Benadryl-hyoscine outcomes are contingent upon such factors as work prolongation, motivation, and supplementary cue feedback.

Secondary Factors Affecting Impairment

It was noted earlier that aeronautic tasks are performed over relatively long periods of time under varying conditions of altitude, task structure, motivation, and other factors upon which the effects of drugs might well be contingent. Consequently, drug studies performed in synthetic situations must have such factors built into their experimental designs whenever possible. Since duration is the most simply managed of all relevant factors, it is not surprising that information concerning it is relatively more abundant.

Hauty and Payne,[8] Payne and Hauty,[15–22] and Ritter[24] have provided conclusive evidence of the interaction of certain drug effects with task duration. For example, Benadryl-hyoscine deficits in multidimensional pursuit are barely detectable for some 60 to 90 minutes following oral administration of the drug, a result that can scarcely be due to absorption latency alone. However, for some two hours thereafter the rate of decrement is vastly more pronounced than that for placebo subjects. Essentially the same result occurs when two individuals under the influence of Benadryl-hyoscine pool their skills in a cooperative task.[24] Moreover, when a drug-duration interaction occurs it applies more or less uniformly to all measurable components of task behavior.[9] By contrast, the action of 0.65 mg. doses of hyoscine alone upon multidimensional pursuit remains negligible throughout a period of at least four hours.[19]

Many of the studies noted above have demonstrated the interaction of drugs with other task conditions. For example, significant adverse effects of hyoscine, Benadryl-hyoscine, and meclizine upon the retention of a serial order verbal task were prevented by increasing the subjects' level of training and motivation to perform.[23] Decrements in multidimensional pursuit under Benadryl-hyoscine conditions were likewise delayed by certain motivational and supplementary cue feedback devices,[8, 22] although such devices were not equally effective.[15, 21]

It is apparent from these interaction studies that task prolongation is an important determinant of the relative adversities of various remedies. There may be others.

Happily, the fact that task duration may work against the usefulness of certain remedies is countered to some extent by the mitigative properties of analeptic drugs,[5] motivational technics, and engineering aids to the extension of human capabilities.

Generalization of Impairment Data

Perhaps the most useful generalization to be drawn from all the studies considered is that a moderate dose of hyoscine presents a minimal, and perhaps negligible, risk of behavioral incapacitation. This is a somewhat familiar generalization, to be sure, but at least it stands clothed now in the respectability of some very substantial experimental work ranging across a broad spectrum of abilities and skills. Dramamine in 100 mg. doses may prove equally acceptable as far as secondary effects are concerned, but adequate studies involving secondary task conditions have not yet been made. Other preparations perhaps should remain in doubt for a time, either because of deleterious effects already noted or because comprehensive studies remain to be done. This is true of Benadryl, the Benadryl-hyoscine mixture, Phenergan, and meclizine. Still newer remedies should not be considered for personnel on airborne duty until adequate performance tests have been accomplished.

FUTURE RESEARCH

Although the work reported here is extensive, the bulk of the problem lies in the future. There are at least five general problems that can and should be pursued vigorously. First, all remedies showing useful prophylaxis of motion sickness should be appraised across a broad spectrum of abilities and skills, and the most promising ones should be studied intensively within certain relevant spectral "bands." Second, repetitive dosage studies are almost nonexistent. Third, dose response nomographs should be constructed for the more important skills so that different quantities of different remedies can be compared on some common ground. There are no behavioral data available for this purpose now. Fourth, the number of studies involving secondary conditions, both mitigative and exacerbative, should be increased, for it is only upon the basis of these that reasonably satisfactory extrapolations from synthetic tasks to "real life" tasks can be made. Finally, there has been a peculiar lack of attention to the effects of motion sickness itself upon abilities and skills. Those who caution against the use of remedies by personnel on airborne duty seem to overlook the possibility that an effective remedy may really be the lesser of two evils. The work of Alexander and his colleagues is to the point.[1] Moreover, there is no work that would show how motion and remedial treatment interact in terms of performance criteria. Obviously there are many attractive possibilities for further work.

BIBLIOGRAPHY

1. Alexander, S. J., et al.: Wesleyan University studies of motion sickness: VII. The effects of sickness upon performance, J. Psychol. 20:31–39, 1945.
2. Bartley, S. H., and Chute, E.: Fatigue and Impairment in Man, New York, McGraw-Hill, 1947.
3. Birren, J. E.; Stormont, R. T., and Fisher, M. B.: Side effects of three motion sickness preventives, Nav. Med. Res. Inst., Res. Proj. X-278, 1944.

4. Corey, E. L., and Webster, A. P.: Effects of scopolamine on marksmanship, Proj. X-213 (Av-Flo-4).
5. Faucett, R. E.: The effects of Dramamine on visual and auditory acuity, USN Med. Res. Lab., New London, Rep. No. 222, 1953.
6. Finan, J. L.; Finan, S. C., and Hartson, L. D.: A review of representative tests used for the quantitative measurements of behavior-decrement under conditions related to aircraft flight, USAF Air Materiel Command, Wright-Patterson AFB, Tech. Rep. No. 5830, 1949.
7. Guilford, J. P. (Ed.): Printed classification tests. Washington: U. S. Government Printing Office, 1947. (AAF Aviation Psychol. Program Res. Rep. No. 5.)
8. Hauty, G. T., and Payne, R. B.: Methods for the mitigation of work decrement, USAF Sch. Aviation Med., Proj. No. 21-1601-0004, Rep. No. 4, 1953.
9. Hauty, G. T., and Payne, R. B.: Effects of work prolongation upon components of a perceptual-motor task, USAF Sch. Aviation Med., Proj. No. 21-1601-0004, Rep. No. 6, 1954.
10. Hauty, G. T., and Payne, R. B.: The effects of an analeptic and a depressant drug upon the error of estimation, USAF Sch. Aviation Med., Proj. No. 47-756-001, Rep. No. 2 (Submitted for publication).
11. Katz, M., and Wendt, G. R.: The effects of hyoscine and Dramamine on vision and hearing. In G. R. Wendt: Final report, studies of motion sickness, vestibular function and of psychological and physiological effects of drugs, 1946–1954. ONR, USN, Proj. No. NR 143-060, 1954.
12. Keil, F. C.: The effect of oral doses of hyoscine (scopolamine) on visual efficiency, USAF Sch. Aviation Med., Proj. No. 157, Rep. No. 1, 1943.
13. Lilienthal, J. L.: The effect of hyoscine on airsickness, J. Aviation Med. *16*:59–68. 1945.
14. MacKay, R. A., and Ferguson, J. K. W.: Influence of certain anti-motion-sickness drugs on psychomotor and mental performance, J. Aviation Med. *22*:194–195, 1951.
15. Melton, A. W. (Ed.): Apparatus tests. Washington: U. S. Government Printing Office, 1947. (AAF Aviation Psychol. Program Res. Rep. No. 4.)
16. Payne, R. B.; Moore, E. W., and Bethurum, J. L.: The effects of certain motion sickness preventives upon psychological efficiency, USAF Sch. Aviation Med., Proj. No. 21-32-019, Rep. No. 1, 1952.
17. Payne, R. B.; Obier, D. R., and Tomlinson, P. A. S.: The effects of certain motion sickness preventives upon navigator proficiency, USAF Sch. Aviation Med., Proj. No. 21-1601-0004, Rep. No. 1, 1953.
18. Payne, R. B., and Hauty, G. T.: The pharmacological control of work output during prolonged tasks, USAF Sch. Aviation Med., Proj. No. 21-1601-0004, Rep. No. 2, 1953.
19. Payne, R. B., and Hauty, G. T.: The effects of motion sickness preventives upon certain perceptual-motor components of the pilot's task, USAF Sch. Aviation Med., Proj. No. 21-1601-0004, Rep. No. 3, 1953.
20. Payne, R. B.: The effects of drugs upon psychological efficiency, J. Aviation Med. *24*:523–529, 1953.
21. Payne, R. B., and Hauty, G. T.: The effects of experimentally induced attitudes upon task proficiency, J. Exper. Psychol. *47*:267–273, 1954.
22. Payne, R. B., and Hauty, G. T.: The influence of drugs, motivation, and job design upon work decrement, USAF Sch. Aviation Med., Proj. No. 47-758-070, Rep. No. 1 (In press).
23. Payne, R. B.: Some psychological factors governing the impairment of verbal retention by cerebral depressants, USAF Sch. Aviation Med., Proj. No. 47-756-001, Rep. No. 1 (In press).
24. Ritter, R. M.: The effects of drugs and controlled motivational feedback upon two-member team behavior, USAF Sch. Aviation Med., Proj. No. 47-755-013, Rep. No. 1 (Submitted for publication).
25. Shock, N. W.: Some psychophysiological relations, Psychol. Bull. *36*:447–476, 1939.
26. Smith, P. K., and Hemminoway, A.: Effects of hyoscine (scopolamine) on swing sickness and on performance, USAF Sch. Aviation Med., Proj. No. 111, Rep. No. 1, 1943.
27. Smith, P. K.: Effects of some central nervous system depressing drugs on intellectual and psychomotor performance at 18,000 feet with and without supplementary oxygen, USAF Sch. Aviation Med., Proj. No. 221, Rep. No. 1, 1944.
28. Smith, P. K.: Effects on swing sickness and side effects of some atropine-like drugs, USAF Sch. Aviation Med., Proj. No. 297, Rep. No. 1, 1945.
29. Spragg, S. D. S.: The effects of certain drugs on mental and motor efficiency, Psychol. Bull. *38*:354–363, 1941.
30. Strickland, B. A.; Hahn, G. L., and Adler, H.: Studies on airsickness, J. Aviation Med. *21*:90–97, 1950.

GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

Roentgen Observation of Carcinoma of the Lung

Presented by LEO G. RIGLER, M.D. (University of Minnesota School of Medicine) before the International College of Surgeons, Chicago, Sept. 8, 1954.

Old chest x-rays of patients with newly diagnosed lung cancer almost always show abnormal shadows in the cancer area. Careful study of all chest x-rays may thus make it possible to recognize many early lung cancers long before symptoms appear, while the disease is more amenable to surgery. Whenever old films could be found, usually made fortuitously, evidence of disease in an area later proved to be due to primary cancer were observed in almost all cases, frequently five or six years before the patient showed any symptoms, and in one instance the evidence of the disease process was present nine years before the actual demonstration of its nature. As a result of the author's study, it was determined that the duration of cancer of the lung from the first evidences of a disease process shown in roentgenograms is much longer than was previously thought.

Cancer of the lung arises in the periphery of the lung much more commonly than was generally thought but tends to grow centrally, so that by the time it is extirpated surgically, or comes to autopsy, it appears to have been present near the center of the lung. Peripheral nodular growths are much more common than was hitherto believed. Certain signs are present in the roentgenogram at a very early stage in the development of the disease; such signs are often minor in character and are readily overlooked.

If lung cancer is to be diagnosed at an early stage, the most minimal changes in the organ must be given serious consideration.

Relation of Thyroid Neoplasms to Hashimoto Thyroiditis

Presented by MORRIS E. DAILEY, M.D., STUART LINDSAY, M.D., AND J. R. SKAHEN, M.D., University of California Hospital, before the American Medical Association, San Francisco, June 22, 1954.

Hashimoto's disease is a noninflammatory disease of the thyroid gland. There is little agreement regarding its pathogenesis; it may be focal or diffuse, and it may occur without thyroid enlargement. Most workers stress the epithelial degenerative changes, but others call attention to islands of solid epithelial tissue with much mitotic activity within them. The authors' studies showed early proliferating cells with pre-existing follicles of the gland which begin to accumulate

colloid. Localized nodular lesions also occur; they appear to be involutional or hyperplastic in some cases. Benign neoplasms show up with Hurthle cell changes. In an irradiated gland (from Graves' disease), histologic section showed multiple benign neoplasms springing from the Hashimoto lesion. Of 36 cases of Hashimoto's disease, 11 showed evidence of Hurthle cell adenoma; this 30 per cent incidence suggests to the authors a significant relationship between the two. In four cases of Hashimoto's disease actual lymphatic invasion with papillary carcinoma was seen without evidence of a primary malignant lesion.

Both adenoma and adenocarcinoma may be found in the same gland; this probably represents independent processes, but both are related to Hashimoto's disease of the gland. Adenocarcinoma may not be suspected clinically; metastasis to local lymph nodes occurs with a lower grade malignancy, usually of the papillary type. Those patients who die of a malignancy associated with Hashimoto's disease do so less frequently and after a longer period of time, i.e., the survival rate is longer.

Streptoduocin in Pulmonary Tuberculosis

Presented by HARRY SHUBIN, M.D.; CHARLES A. HEIKEN, M.D.; ALLEN GLASKIN, M.D.; EDWARD PENNES, M.D.; SUSHIL CHAKRAVARTY, M.D., AND FRANKLIN RUTBERG, M.D., Philadelphia General Hospital, before the American College of Chest Physicians, June 20, 1954.

Streptoduocin is defined as a mixture of equal parts (0.5 Gm. of each) of streptomycin and dihydrostreptomycin. This combination resulted from an attempt to reduce the eighth nerve toxicity of the two compounds; by using this combination, the dosage of each drug is reduced by one-half. This study included 136 patients in whom two regimens were instituted: In the first, 1 Gm. of streptoduocin was given daily; in the second, streptoduocin was given twice a week. The following results were obtained:

	Vestibular Damage		*Cochlear Damage*	
First Study	*Daily*	*2nd Week*	*Daily*	*2nd Week*
Streptomycin	30%	5%	6%	0.5%
Dihydrostreptomycin	5%	1%	26%	4%
Streptoduocin	0%	0%	0%	0%
Second Study				
106 patients				
Streptomycin		6%		0.5%
Dihydrostreptomycin		1%		6%
Streptoduocin		1%		0%

The clinical results obtained were similar, but the toxic effects were practically eliminated when streptoduocin was used. Streptoduocin was tried in conjunction with isoniazid or p-aminosalicylic acid on patients who already had manifestations of eighth nerve toxicity. Of the 24 patients in this group, each was given streptoduocin after a two week rest period from all previous drug therapy. It was found that there was no further increase in toxicity nor in auditory or vestibular damage, while typical beneficial effects continued.

CANCER—PREVENTION AND CURE

The problem of cancer continues to present the medical and allied professions with their most provocative challenge. In the lay mind there undoubtedly lurks a latent resentment at the alleged failure of medical science to find a "cure" for this dreaded disease. Many physicians themselves feel discouraged by a problem whose complexity now involves biochemists, biophysicists and many other research specialists. Where does medical science stand today?

A significant finding in the last twenty years is that while most types of cancer have either remained statistically stationary or increased only moderately, the incidence of bronchogenic carcinoma has increased more than threefold in several urban-industrial countries. Some sensationalized surveys here and in England[1, 2] have related this statistical fact to the use of tobacco, particularly in the form of cigarettes. In the past five years, more than a dozen surveys have indicated that there are more heavy or excessive smokers among lung cancer patients than in the general population, the predominant increase being among males living in cities. On the other hand, it has also been suggested that the increase in bronchogenic carcinoma might be correlated with the extensive pollution of urban-industrial atmospheres.[3] How do these data accord with our present concepts of carcinogenesis?

Morphologic Change

There is now general agreement that cancer is the result of some irreversible biologic change in a cell, caused by an exogenous or endogenous "stress" on the cell's normal metabolism. This stress may be mechanical irritation, as in the case of lungs exposed to metal dust, wood dust or other solid aerosols. It may be chemical, as shown in the high incidence of lung cancer among persons subjected to hydrocarbon or arsenical fumes.[4, 5] The relationship between sunlight or other types of radiation and epidermoid cancer is well established, as is the sinister tie between roentgen rays and leukemia. And there exists a quantity of clinical data linking the growth or acceleration of certain types of cancer to androgenic or estrogenic hormones.

This poses one of the most tantalizing problems in cancer research: are known carcinogenic substances causative or merely supportive agents in the transformation of normal cells into malignant ones? There is undoubtedly an abnormally high incidence of lung cancer among workers in the chromate industry, but the largest proportion of these workers do not develop tumors. Equally, the great majority of heavy smokers do not die of cancer. Could this indicate that certain human cells are "predisposed" to malignancy and thus more sensitive to the effect of some environmental stress?[6] This problem was thoroughly discussed at the recent 6th International Cancer Congress held in Brazil, and it also animates the work of the German Research Council (Deutsche Forschungsgemeinschaft) which

since 1949 has been studying means of protecting humans against carcinogenic substances in the environment and food.

The principal difficulty in the prevention and cure of cancer apparently lies in the time factor. Minute doses of some carcinogenic substance or radiation, which have no discernible effect on tissues, may build up a summative effect over a long period. In the case of lung carcinoma, one opinion is that the primary irreversible change occurs in youth and then requires some 20 or 30 years to grow into a diagnosable tumor. Another view is that the histologic and endocrinal degeneration that accompanies age is the responsible endogenous factor in malignancy. The peak incidence of most types of carcinoma between the ages of 50 and 65 certainly appears to support the latter school of thought.

Progress in Therapy

Meanwhile, the therapy of cancer continues to progress. Cytologic diagnosis has made rapid strides since the pioneer work of Papanicolau, particularly in the treatment of female genital carcinomas. The use of radioisotopes holds some promise, although many initial experiments have proved disappointing. The combined effect of castration, adrenalectomy, and hormone therapy has given encouraging results in the treatment of cancer of the prostate and of the female breast. Intense laboratory research promises to discover more means of destroying cancer cells with antimetabolites such as 6-mercaptopurine; the treatment of leukemia in children with a combination of amethopterine, cortisone, and 6-mercaptopurine has already shown a significant increase in survival rate. And radiation therapy continues to produce curative or palliative results; the most recent development in that field being the use of "super-voltage" machines to deliver massive tumor doses.

The outlook for the prevention and cure of cancer is therefore far from gloomy. Our understanding of environmental carcinogens has grown vastly in the last ten years, particularly in regard to airborne pollutants, food additives, and dyes. The metabolic habits of cancer cells, compared with those of normal ones, are being better understood every year. New chemotherapeutic agents now being developed in laboratories will soon pass into general clinical use. The "prognosis" for 1955 is consequently very encouraging.

REFERENCES

1. Hammond, E. C., and Horn, D.: The Relationship Between Human Smoking Habits and Death Rate, J. A. M. A. *155*:1316 (Aug. 17) 1954.
2. Doll, R., and Hill, A. B.: The Mortality of Doctors in Relation to Their Smoking Habits, Brit. M. J. *1*:1451 (June 26) 1954.
3. Kotin, P.; Falk, H. L.; Mader, P., and Thomas, M.: Aromatic Hydrocarbons I. Presence in the Los Angeles Atmosphere and the Carcinogenicity of Atmospheric Extracts, Arch. Indust. Hyg. *9*:153 (Feb.) 1954.
4. Breslow, L.; Hoaglin, L.; Rasmussen, G., and Abrams, H.: Occupations and Cigarette Smoking as Factors in Lung Cancer, Am. J. Pub. Health. *44*:171 (Feb.) 1954.
5. Wynder, E. L., and Graham, E. A.: Etiologic Factors in Bronchiogenic Carcinoma with Special Reference to Industrial Exposures: a Report of 857 Proved Cases, Arch. Indust. Hyg. *4*:221 (Sept.) 1951.
6. Ahlbom, H. E.: Prädisponierende Faktoren für Plattenepithelkarzinom im Mund, Hals und Speiseröhre, Eine Statistische Untersuchung am Material des Radiumhemmets, Acta radiol. *18*:163, 1937.

EDUCATION FOR GENERAL PRACTICE

Medical societies and other professional groups throughout the English-speaking world are at present engaged in a thorough discussion of medical education. The two problems in the forefront of attention are pre-medical curriculae and the type of undergraduate training required to produce good general practitioners.

It is generally agreed that the last two years of school are important in orienting students towards their eventual profession, but here we meet a divergence of views. Should pre-medical students be given intensive training in such subjects as chemistry, physics, biology, and zoology, or should they receive a broader education in the liberal arts? British medical circles appear to feel that the undergraduate training of family physicians is unsatisfactory.[1] In a widespread discussion by medical practitioners and faculty boards, organized by the College of General Practitioners, only a few physicians favored early scientific specialization. Many expressed doubt whether the aspiring physician needs to know as much organic and inorganic chemistry, physics, and zoology as some universities require in pre-medical courses. The great majority favored a liberal education for a liberal profession, echoing the words of SIR RICHARD LIVINGSTONE: "Knowledge is important . . . but most important of all is what a man believes . . . whether he has clear values and standards and is prepared to live by them."[2]

Liberal Education

This liberal approach appears to be growing also in the United States. It was reported at the First World Conference on Medical Education in 1953 that two significant trends were having a profound effect on the American pre-medical college curriculum. These were, firstly, a strong movement for a return to liberal or general education for all students and, secondly, a pronounced emphasis on the social sciences. SEVERINGHAUS, of Columbia University, noted at this same Conference that an expanding materialistic philosophy in the present century forced many colleges to concentrate on technical "training for the job." But American education authorities are now asking whether the great synthesizing disciplines of history, philosophy, and religion have too long been neglected in the education of aspiring physicians.[3]

Debate continues. In the British series of discussions, some regional faculties complained that too much time in the curriculum of medical students was devoted to specialties, such as anatomy and advanced surgery. LORD HORDER doubts whether the budding "family doctor" needs to have an intimate knowledge of the organ of Corti, and he goes on: "I think we took a step backwards when we put the academic anatomist, physiologist, and chemist in charge of preclinical studies. These men staked out large claims in their respective spheres as though medical students were in training for professorships in these subjects rather than being doctors in embryo."[4] A similar objection appears to be valid in Canada, Australia, and many parts of the United States.

On one point there seems to be agreement on both sides of the Atlantic, namely that there is a great need for "family doctors" and that this branch of medicine requires special training. Technical skill and a hospital internship are not enough. The medical undergraduate should learn from the start that patients are not just "cases" on the ward or in the out-patient department, but living human beings who require a continuity of attention throughout life. One consultant in a London teaching hospital always takes a student with him in his domiciliary visits; in Edinburgh, students are encouraged to attend at health centers where they can familiarize themselves with the common diseases that afflict the poorer segments of humanity; in some British hospitals, general practitioners are invited as lecturers. The time spent in such ways would seem to be more fruitful than a discussion of the current theories of color vision.

The objectives of medical education are well summed up in the report of the Association of American Medical Colleges, where it was urged that undergraduate medical schools "must strive to help the student to acquire basic professional knowledge; establish essential habits . . . and develop those basic intellectual attitudes and ethical and moral principles which are essential if he is to gain and maintain the confidence and trust of those whom he treats, the respect of those with whom he works and the support of the community in which he lives."

REFERENCES

1. Report of the Undergraduate Education Committee of the First Council of the College of General Practitioners. Brit. M. J. *1*:1146, May 15, 1954.
2. Livingstone, Sir Richard: *Education for a World Adrift*, 1943, Cambridge University Press.
3. Severinghaus, A. E.: Selection of Students in the United States, Brit. M. J. *2*:482, Aug. 28, 1954.
4. Horder, Lord: Brit. M. J. *2*:1359, 1951.
5. Association of American Medical Colleges: The Objectives of Undergraduate Medical Education, J. M. Educ. *28*:57, March, 1953.

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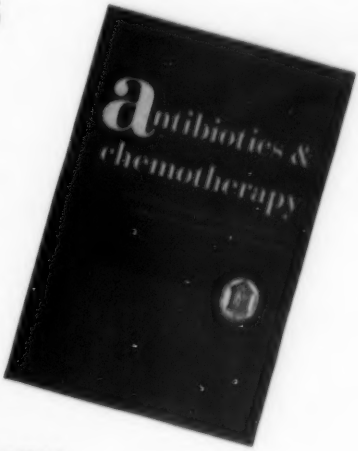

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